

polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chondritis, cochitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis,

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encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues.

Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively,

polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

5           In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

10           In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art.

15           In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected  
20           from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

                  In another specific embodiment, polypeptides, antibodies, polynucleotides  
25           and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments,  
30           the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseria meningitidis*,  
5 *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may  
10 be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an  
15 immune response to Plasmodium (malaria) or Leishmania.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear  
20 phagocytes.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

25 In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and  
30 immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.



In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of  
10 immunosuppressive therapies.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

15 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system  
25 enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the  
30 beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the

beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost  
5 immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

10 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists  
15 or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

In another specific embodiment, polypeptides, antibodies, polynucleotides  
20 and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement  
25 or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e.  
30 TH2) as opposed to a TH1 cellular response.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce

tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

5           In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

10           In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

15           In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

20           In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

25           In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

          In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications described herein, as they may apply to veterinary medicine.

30           In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may

be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

10 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

15 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described  
25 herein and include multiple sclerosis, and insulin-dependent diabetes.

The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

30 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

10 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of  
15 the invention may be used to stimulate the regeneration of mucosal surfaces.

In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover,  
20 polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases,  
25 disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or  
30 polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). polypeptides,

antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

In another embodiment, polypeptides, antibodies, polynucleotides and/or  
5 agonists or antagonists of the present invention are administered to an animal  
(including, but not limited to, those listed above, and also including transgenic  
animals) incapable of producing functional endogenous antibody molecules or having  
an otherwise compromised endogenous immune system, but which is capable of  
producing human immunoglobulin molecules by means of a reconstituted or partially  
10 reconstituted immune system from another animal (see, e.g., published PCT  
Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741).  
Administration of polypeptides, antibodies, polynucleotides and/or agonists or  
antagonists of the present invention to such animals is useful for the generation of  
monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or  
15 agonists or antagonists of the present invention in an organ system listed above.

### **Blood-Related Disorders**

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists  
of the present invention may be used to modulate hemostatic (the stopping of  
20 bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing  
hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists  
or antagonists of the present invention could be used to treat or prevent blood  
coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor  
deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g.,  
25 thrombocytopenia), or wounds resulting from trauma, surgery, or other causes.  
Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or  
antagonists of the present invention that can decrease hemostatic or thrombolytic  
activity could be used to inhibit or dissolve clotting. These molecules could be  
important in the treatment or prevention of heart attacks (infarction), strokes, or  
30 scarring.

In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or  
agonists or antagonists of the present invention may be used to prevent, diagnose,

prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B, column 8 (Tissue Distribution Library Code).

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g.,



basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

5           The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

          Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased  
10   red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or  
15   antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary sideroblastic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune hemolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides,  
20   polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the  
25   present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyl dopa, dapsone, and/or sulfadruugs. Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture  
30   including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the

5 polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or

10 agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak

15 syndromes, thromboxane A2 dysfunction, thromboasthenia; and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophilia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorrhagic Telangiectasia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

20 The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or

25 the Lee-White Clotting time.

Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction

30 accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug

treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing,

5 prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body  
10 generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer.

Leukocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides,

15 antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

20 Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia.

25 Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency),

30 neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias

resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

- 5           The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndrome, severe combined immunodeficiency, ataxia telangiectasia).

- 10           The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

- 15           In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

- 20           In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphoblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukemia), chronic myelocytic (myeloid, myelogenous, or granulocytic)
- 25
- 30

leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

10 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myeloid metaplasia, thrombocythemia, (including both primary and secondary thrombocythemia) and chronic myelocytic leukemia.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

20 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosinophils and macrophages.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

30 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

## 5 **Hyperproliferative Disorders**

In certain embodiments, polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder  
10 through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating,  
15 differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

20 Examples of hyperproliferative disorders that can be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and  
25 peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute  
30 Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute

- Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct
- 5 Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia,
- 10 Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma,
- 15 Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer,
- 20 Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational
- 25 Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer,
- 30 Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous

Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's

5 Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic

10 Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary

15 Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal

20 Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

In another preferred embodiment, polynucleotides or polypeptides, or agonists

25 or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia,

30 metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)



Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic

ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atridigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, 5 craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, 10 florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, 15 oculovertebral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

Additional pre-neoplastic disorders which can be diagnosed, prognosed, 20 prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

25 In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B, column 8 (Tissue Distribution Library Code).

30 In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including,

but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

5           Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated  
10 by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma,  
15 lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related  
20 glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

          In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis  
25 of cancers, in particular those listed above.

          Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such  
30 as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic

(granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, 5 liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland 10 carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, 15 glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or 20 agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, 25 polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin- 30 induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Another preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention

inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for

polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell-proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some

of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

5           In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

10           The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

          It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or  
15   neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments  
20   thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-6}M$ ,  $10^{-6}M$ ,  $5 \times 10^{-7}M$ ,  $10^{-7}M$ ,  $5 \times 10^{-8}M$ ,  $10^{-8}M$ ,  $5 \times 10^{-9}M$ ,  $10^{-9}M$ ,  $5 \times 10^{-10}M$ ,  $10^{-10}M$ ,  $5 \times 10^{-11}M$ ,  $10^{-11}M$ ,  $5 \times 10^{-12}M$ ,  $10^{-12}M$ ,  $5 \times 10^{-13}M$ ,  $10^{-13}M$ ,  $5 \times 10^{-14}M$ ,  $10^{-14}M$ ,  $5 \times 10^{-15}M$ , and  $10^{-15}M$ .

          Moreover, polypeptides of the present invention are useful in inhibiting the  
25   angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl  
30   Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al.,



Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide

antibodies of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

### **Renal Disorders**

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal

artery embolism, and renal artery stenosis), and kidney disorders resulting from urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

- 5           In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome,
- 10       polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE),
- 15       Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

- Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis
- 20       (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia,
- 25       hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

- Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle
- 30       accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the

art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

## 5 **Cardiovascular Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

10 Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia,  
15 patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilog y of Fallot, ventricular heart septal defects.

20 Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy,  
25 right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar  
30 Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-

branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular  
5 rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse,  
10 tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular  
15 stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include, but are not limited to, coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis,  
20 coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive  
25 diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena  
30 cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include, but are not limited to, dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include, but are not limited to, coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or

topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

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### **Respiratory Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

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Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumococcal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomonas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

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Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis, fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal

infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia* spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

### **Anti-Angiogenesis Activity**

The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization



including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, *Medicine*, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and

Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists  
5 may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in  
10 treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular  
15 glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations;  
20 ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a  
25 polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This  
30 therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress

(approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, 5 retrolental fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of 10 prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalm.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalm.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for 15 treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, 20 capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes 25 simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared 30 for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and

administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the

compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the polynucleotides, polypeptides, agonists and/or antagonists of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals,

arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation

- 5 controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (*Rochela minalia quintosa*), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and  
10 fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

- 15 Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present  
20 invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat  
25 tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized  
30 during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or antagonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or antagonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or antagonists of the present invention may also be administered along with other anti-angiogenic factors.

Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl

complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten  
 5 oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its  
 10 hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and  
 15 sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan  
 20 Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin;  
 25 Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum;  
 30 alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-



316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolimidazole; and metalloproteinase inhibitors such as BB94.

### **Diseases at the Cellular Level**

- 5 Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors,
- 10 pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's
- 15 syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.
- 20 In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

- Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or
- 25 antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic
- 30 lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and

carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

### **Wound Healing and Epithelial Cell Proliferation**

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to

stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical  
5 wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications  
10 associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the  
15 present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown  
20 grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or  
25 antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach,  
30 small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes,

mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

5 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides,  
10 as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat  
15 glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides,  
20 as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large  
25 intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the  
30 production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

### **Neural Activity and Neurological Diseases**

The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be

5 treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian

10 patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including

15 lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of

20 the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration

25 associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia,

30 Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy),

systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human  
5 immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects  
10 of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the  
15 polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

20 In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

25 In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

30 The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of

limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, 10:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, 70:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, 4:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists



or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such

5 neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition,

10 compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage,

15 disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus

20 thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

25 In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore,

polynucleotides, polypeptides, agonists and/or antagonists of the invention may be

30 used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral

encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, 5 encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden- 10 Spatz Syndrome.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral 15 malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine 20 Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis 25 which includes lymphocytic choriomeningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uveomeningoencephalitic syndrome, myelitis such as 30 transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as

Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention

5 include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral  
10 sclerolosis which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue  
15 Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's  
20 Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon-Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett  
25 Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

30 Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie

Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, 5 apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, 10 broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, 15 myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic 20 Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, 25 spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, 30 Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia,

amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes

- 5 Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis,
- 10 Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.
- 15 Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial
- 20 neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies
- 25 which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

### **Endocrine Disorders**

- 30 Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine

system.

Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

In specific embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists of those polypeptides (including antibodies) as well as fragments and variants of those polynucleotides, polypeptides, agonists and antagonists, may be used to diagnose, prognose, treat, prevent, or ameliorate diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells.

In a specific embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type I diabetes mellitus (insulin dependent diabetes mellitus, IDDM).

In another embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type II diabetes mellitus (insulin resistant diabetes mellitus).

Additionally, in other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or antagonists thereof (especially neutralizing or antagonistic antibodies) may be used to diagnose, prognose, treat, prevent, and/or ameliorate conditions associated with (type I or type II) diabetes mellitus, including, but not limited to, diabetic ketoacidosis, diabetic coma, nonketotic hyperglycemic-hyperosmolar coma, seizures, mental confusion, drowsiness, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section), dyslipidemia, kidney disease (e.g., renal failure, nephropathy other diseases and disorders as described in the "Renal Disorders" section), nerve damage, neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture.

In other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to regulate the animal's weight. In specific embodiments the polynucleotides and/or polypeptides



corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin. In still other embodiments the polynucleotides and/or polypeptides corresponding to this gene  
5 and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin-like growth factor.

In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including  
10 cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

Moreover, endocrine system and/or hormone imbalance disorders and/or  
15 diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

In another embodiment, a polypeptide of the invention, or polynucleotides,  
20 antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B, column 8 (Tissue Distribution Library Code).

25

### **Reproductive System Disorders**

The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be  
30 treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and

diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid papulosis, giant condyloma of Buscke-Lowenstein, and verrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

Moreover, diseases and/or disorders of the vas deferens include vasculitis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, leiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a

non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelphys, and T-shaped uterus.

Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometrioid carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus erythematosus, rheumatoid arthritis, myasthenia

gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders, and obstruction of the intestine.

Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that  
5 progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis,  
10 pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and agonists or antagonists of the present invention include, for example, Turner's  
15 syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

### **Infectious Disease**

20 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by  
25 initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or  
30 agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae,

Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papilloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases; skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention; can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., *Nocardia*), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthracis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candida, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium difficile*,

*Clostridium perfringens*, *Clostridium tetani*), *Coccidioides*, *Corynebacterium* (e.g., *Corynebacterium diphtheriae*), *Cryptococcus*, *Dermatocycoses*, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), *Enterobacter* (e.g., *Enterobacter aerogenes*), *Enterobacteriaceae* (*Klebsiella*, *Salmonella* (e.g.,

5 *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), *Serratia*, *Yersinia*, *Shigella*), *Erysipelothrix*, *Haemophilus* (e.g., *Haemophilus influenza* type B), *Helicobacter*, *Legionella* (e.g., *Legionella pneumophila*), *Leptospira*, *Listeria* (e.g., *Listeria monocytogenes*), *Mycoplasma*, *Mycobacterium* (e.g., *Mycobacterium leprae* and *Mycobacterium tuberculosis*), *Vibrio* (e.g., *Vibrio cholerae*), *Neisseriaceae* (e.g.,

10 *Neisseria gonorrhea*, *Neisseria meningitidis*), *Pasteurellaceae*, *Proteus*, *Pseudomonas* (e.g., *Pseudomonas aeruginosa*), *Rickettsiaceae*, *Spirochetes* (e.g., *Treponema* spp., *Leptospira* spp., *Borrelia* spp.), *Shigella* spp., *Staphylococcus* (e.g., *Staphylococcus aureus*), *Meningioccus*, *Pneumococcus* and *Streptococcus* (e.g., *Streptococcus pneumoniae* and Groups A, B, and C *Streptococci*), and *Ureaplasmas*. These

15 bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as

20 Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, *Legionella* disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., meningitis types A and B), chlamydia, syphilis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung

25 infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections,

30 noscomial infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In

specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, diphtheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, 5 Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Schistosoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparum*, *Plasmodium malariae* and 10 *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be 15 used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose malaria.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an 20 effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### **Regeneration**

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of 30 tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis,



osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal  
5 or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For  
10 example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of  
15 non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated  
20 using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases  
25 (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

### 30 **Gastrointestinal Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal

disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowel lymphoma)), and ulcers, such as peptic ulcers.

5           Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric  
10 stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

15           Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of  
20 complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

25           Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic,  
30 biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver

enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic

5 encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial

10 tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile

15 hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma,

20 cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger

25 syndrome).

Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other

30 pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

Diseases and/or disorders of the large intestine include antibiotic-associated  
5 colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases  
10 [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases  
15 (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal  
20 volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal  
25 lymphangiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia,  
30 gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach

rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

### **Chemotaxis**

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These

chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

### **Binding Activity**

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

5 Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a  
10 standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

15 Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides,  
20 for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labeled. The  
25 polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually  
30 yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express

the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would  
5 be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention  
10 thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R.  
15 *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides  
20 and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains,  
25 fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7,  
30 activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation



factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity  
5 similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention.  
10 An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and  $^3\text{[H]}$  thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the  
15 compound to determine if the compound stimulates proliferation by determining the uptake of  $^3\text{[H]}$  thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of  $^3\text{[H]}$  thymidine. Both agonist and antagonist compounds may be identified by this procedure.

20 In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following  
25 interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

30 All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring

about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

- 5           Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate
- 10   compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

### **Targeted Delivery**

- 15           In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

- As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or
- 20   prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic
- 25   protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

- In another embodiment, the invention provides a method for the specific
- 30   destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

### **Drug Screening**

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation

of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

### 30 **Polypeptides of the Invention Binding Peptides and Other Molecules**

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the

polypeptide of the invention binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

5           This method comprises the steps of: contacting a polypeptide of the invention with a plurality of molecules; and identifying a molecule that binds the polypeptide of the invention.

          The step of contacting the polypeptide of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate  
10   immobilizing the polypeptide of the invention on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptide of the invention. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptide of the invention. The molecules having a selective affinity for the polypeptide of the  
15   invention can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptide of the invention to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

          Alternatively, one may also separate a plurality of polypeptides into  
20   substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant  
25   phage). Individual isolates can then be "probed" by the polypeptide of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptide of the invention and the individual clone. Prior to contacting the polypeptide of the invention with each fraction comprising individual polypeptides, the polypeptides  
30   could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of

transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for a polypeptide of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptide of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound polypeptide of the invention, or alternatively, unbound polypeptides, from a mixture of the polypeptide of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the polypeptide of the invention or the plurality of polypeptides is bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind to a polypeptide of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, *Science* 251:767-773; Houghten et al., 1991, *Nature* 354:84-86; Lam et al., 1991, *Nature* 354:82-84; Medynski, 1994, *Bio/Technology* 12:709-710; Gallop et al., 1994, *J. Medicinal Chemistry* 37(9):1233-1251; Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; Salmon et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, *Proc. Natl. Acad. Sci. USA* 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, *Science* 249:386-390; Devlin et al., 1990, *Science*, 249:404-406; Christian, R. B., et al., 1992, *J. Mol. Biol.* 227:711-718; Lenstra, 1992, *J. Immunol. Meth.* 152:149-157;

Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis  
5 et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide  
10 functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list  
15 benzodiazepines, hydantoins, piperazinediones, biphenyls; sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated  
20 monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are  
25 assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer  
30 libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992, *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, *Science* 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds a polypeptide of the invention can be carried out by contacting the library members with a polypeptide of the invention immobilized on a solid phase and harvesting those library members that bind to the polypeptide of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, *Gene* 73:305-318; Fowlkes et al., 1992, *BioTechniques* 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, *Nature* 340:245-246; Chien et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:9578-9582) can be used to identify molecules that specifically bind to a polypeptide of the invention.

Where the polypeptide of the invention binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine.



Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

5       As mentioned above, in the case of a polypeptide of the invention binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a polypeptide of the invention binding polypeptide has in the range of 15-100 amino acids, or 20-50  
10   amino acids.

The selected polypeptide of the invention binding polypeptide can be obtained by chemical synthesis or recombinant expression.

#### **Antisense And Ribozyme (Antagonists)**

15       In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered  
20   (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense  
25   Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research, 6:3073 (1979); Cooney et al., Science, 241:456 (1988); and Dervan et al., Science, 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

30       For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These

experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl<sub>2</sub>, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding a polypeptide of the invention, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature*, 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell*, 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.*, 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster et al., *Nature*, 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of interest. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a  
5 sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the  
10 hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, *e.g.*,  
15 the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature*, 372:333-335 (1994). Thus, oligonucleotides complementary to either the 5' - or 3' -  
20 non- translated, non-coding regions of a polynucleotide sequence of the invention could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but  
25 could be used in accordance with the invention. Whether designed to hybridize to the 5' -, 3' - or coding region of mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

30 The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or

phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556 (1989); Lemaitre et al., *Proc. Natl. Acad. Sci.*, 84:648-652 (1987); PCT Publication NO: WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication NO: WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., *BioTechniques*, 6:958-976 (1988)) or intercalating agents. (See, e.g., Zon, *Pharm. Res.*, 5:539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited

to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., Nucl. Acids Res., 15:6625-6641 (1987)). The oligonucleotide is a 2-O-methylribonucleotide (Inoue et al., Nucl. Acids Res., 15:6131-6148 (1987)), or a chimeric RNA-DNA analogue (Inoue et al., FEBS Lett. 10 215:327-330 (1987)).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. 15 (Nucl. Acids Res., 16:3209 (1988)), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., Proc. Natl. Acad. Sci. U.S.A., 85:7448-7451 (1988)), etc.

While antisense nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated 20 region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs 25 corresponding to the polynucleotides of the invention, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5' -UG-3'. The construction and production of hammerhead ribozymes is well 30 known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably,

the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the polynucleotides of the invention; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

5           As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A  
10       preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular  
15       concentration is required for efficiency.

          Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation  
20       or growth.

          The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirable in cases such as restenosis after balloon  
25       angioplasty.

          The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

          The antagonist/agonist may also be employed to treat, prevent, and/or diagnose the diseases described herein.

30       Thus, the invention provides a method of treating or preventing diseases, disorders, and/or conditions, including but not limited to the diseases, disorders, and/or conditions listed throughout this application, associated with overexpression of

a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

invention, and/or (b) a ribozyme directed to the polynucleotide of the present  
5 invention

### **Other Activities**

The polypeptide of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as  
10 thrombosis, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

The polypeptide may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells  
15 of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

The polypeptide of the present invention may also be employed stimulate neuronal growth and to treat, prevent, and/or diagnose neuronal damage which occurs  
20 in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. The polypeptide of the invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

25 The polypeptide of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

The polypeptide of the invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, the polypeptides of the present invention may be  
30 employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

The polypeptide of the invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues.

The polypeptide of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

5       The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

10       The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, polypeptides or polynucleotides and/or agonist or antagonists of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

15       A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to treat weight disorders, including but not limited to, obesity, cachexia, wasting disease, anorexia, and bulimia.

20       Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive diseases, disorders, and/or conditions), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

25       Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

### **Other Preferred Embodiments**

30       Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95%



identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of  
5 positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of  
10 positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the  
15 range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide  
20 sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

25 A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X  
30 in Table 1A.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under  
5 stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which  
10 comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1A, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1A for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide  
15 sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1A, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1A.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of  
20 at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

25 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule  
30 comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least

one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1A, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human

cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of:

an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

5 Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules  
10 in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in  
15 Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid  
20 sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted  
25 protein identified in Table 1A, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10  
30 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a secreted protein encoded by a human cDNA

clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

- 5           Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y
- 10       wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

- Also preferred is an isolated nucleic acid molecule, wherein said nucleotide
- 15       sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

- Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and
- 20       a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

- Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred
- 25       is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

- Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is
- 30       expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an



amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1A and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1A; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

## **Examples**

### **Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample**

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1A identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below

correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1A as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

5	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
	Zap Express	pBK
	lafmid BA	plafmid BA
10	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
	pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1
15	<p>Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are</p>	
20	<p>commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3</p>	
25	<p>primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.</p>	
30	<p>Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain</p>	

DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1A, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1A for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1A. Typically, each ATCC deposit sample cited in Table 1A comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1A. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with <sup>32</sup>P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection

agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1A) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 ul of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl<sub>2</sub>, 0.01% (w/v) gelatin, 20 uM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should  
5 then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA  
10 synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

### **Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide**

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR  
using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

### **Example 3: Tissue Distribution of Polypeptide**

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method  
25 described in Example 1 is labeled with P<sup>32</sup> using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA  
30 expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled

probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70 degree C overnight, and the films developed according to standard procedures.

5

#### **Example 4: Chromosomal Mapping of the Polynucleotides**

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95 degree C; 1 minute, 56 degree C; 1 minute, 70 degree C. This cycle is repeated 32 times followed by one 5 minute cycle at 70 degree C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

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#### **Example 5: Bacterial Expression of a Polypeptide**

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

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The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain

M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>).

Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4 degree C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50

mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4 degree C or frozen at -80 degree C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an *E. coli* origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718.(3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

#### **Example 6: Purification of a Polypeptide from an Inclusion Body**

The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10 degree C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10 degree C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.



The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4 degree C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4 degree C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 um membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 ug of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

### **Example 7: Cloning and Expression of a Polypeptide in a Baculovirus**

#### **Expression System**

10 In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the 15 plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide. 20

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as 25 required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1A, is amplified using the PCR protocol described in Example 1. If the 30 naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard

methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a  
5 commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine  
10 procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation  
15 mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five ug of a plasmid containing the polynucleotide is co-transfected with 1.0  
20 ug of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One ug of BaculoGold™ virus DNA and 5 ug of the plasmid are mixed in a sterile well of a microtiter plate containing 50 ul of serum-free Grace's medium (Life Technologies  
25 Inc., Gaithersburg, MD). Afterwards, 10 ul Lipofectin plus 90 ul Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27 degrees C. The transfection solution is then removed  
30 from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27 degrees C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 ul of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4 degree C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 uCi of  $^{35}\text{S}$ -methionine and 5 uCi  $^{35}\text{S}$ -cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

#### **Example 8: Expression of a Polypeptide in Mammalian Cells**

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening

sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be  
5 used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used  
10 include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a  
15 selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of  
20 interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers,  
25 the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the  
30 expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the

CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 a pC4 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50

nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 uM, 2 uM, 5 uM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a  
5 concentration of 100 - 200 uM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

### **Example 9: Protein Fusions**

The polypeptides of the present invention are preferably fused to other  
10 proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to  
15 IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create  
20 chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These  
25 primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with  
30 BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note

that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a  
5 heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

```
GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCACC
10 GTGCCCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCG
TGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTAC
GTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC
AGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
15 GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
CCCAACCCCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGA
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAA
CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCG
CCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCAC
20 GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC
CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGA
TGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT
CCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)
```

#### 25 **Example 10: Production of an Antibody from a Polypeptide**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred  
30 method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.



In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56 degrees C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 ug/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

#### **Example 11: Production Of Secreted Protein For High-Throughput Screening Assays**

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described herein.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine

(12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate.

- 5 With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45
- 10 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

- Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too
- 15 much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degrees
  - 20 C for 6 hours.

- While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>·5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>·7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of
- 25 NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>·7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of
  - 30 Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-

2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0  
5 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319  
10 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin  
15 complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

20 The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degrees C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml  
25 deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing  
30 expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

**Example 12: Construction of GAS Reporter Construct**

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

- Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using
- 5 GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

			<u>JAKs</u>				<u>STATS</u>	<u>GAS(elements) or ISRE</u>
	<u>Ligand</u>		<u>tyk2</u>	<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>		
	<u>IFN family</u>							
5	IFN- $\alpha$ /B	+	+	-	-	1,2,3		ISRE
	IFN-g			+	+	-	1	GAS (IRF1>Lys6>IFP)
	IL-10		+	?	?	-	1,3	
	<u>gp130 family</u>							
10	IL-6 (Pleiotrophic)		+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	IL-11(Pleiotrophic)		?	+	?	?	1,3	
	OnM(Pleiotrophic)		?	+	+	?	1,3	
	LIF(Pleiotrophic) ?		+	+	?	1,3		
	CNTF(Pleiotrophic)	-/+	+	+	+	?	1,3	
15	G-CSF(Pleiotrophic)		?	+	?	?	1,3	
	IL-12(Pleiotrophic)		+	-	+	+	1,3	
	<u>g-C family</u>							
20	IL-2 (lymphocytes)		-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid)		-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)		-	+	-	+	5	GAS
	IL-9 (lymphocytes)		-	+	-	+	5	GAS
	IL-13 (lymphocyte)		-	+	?	?	6	GAS
	IL-15		?	+	?	+	5	GAS
25	<u>gp140 family</u>							
	IL-3 (myeloid)		-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)		-	-	+	-	5	GAS
	GM-CSF (myeloid)		-	-	+	-	5	GAS
30	<u>Growth hormone family</u>							
	GH		?	-	+	-	5	
	PRL		?	+/-	+	-	1,3,5	
	EPO		?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
35	<u>Receptor Tyrosine Kinases</u>							
	EGF		?	+	+	-	1,3	GAS (IRF1)
	PDGF		?	+	+	-	1,3	
	CSF-1		?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

10        5':GCGCCTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATGATTTCCTCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTTGCAAAGCCTAGGC:3'

15        (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

20        5':CTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATGATTTCCTCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCCA  
TTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGC  
25        CGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTTGGAGGCCTAGGCTTTTTGCAAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol



acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using Sall and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

### **Example 13: High-Throughput Screening Assay for T-cell Activity.**

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152),

although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-  
5 SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is  
10 demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1% Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life  
15 Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25  
20 flask and incubate at 37 degrees C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptides of the invention and/or induced polypeptides of  
25 the invention as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100  
30 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100,000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred  
5 directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed  
10 in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophane covers) and stored at -20 degrees C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4 degrees C and serve  
15 as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as,  
20 stable transfected cells, which would be apparent to those of skill in the art.

#### **Example 14: High-Throughput Screening Assay Identifying Myeloid Activity**

The following protocol is used to assess myeloid activity by determining whether polypeptides of the invention proliferates and/or differentiates myeloid cells.  
25 Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct  
30 produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing

10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM  
5 KCl, 375 uM Na<sub>2</sub>HPO<sub>4</sub>·7H<sub>2</sub>O, 1 mM MgCl<sub>2</sub>, and 675 uM CaCl<sub>2</sub>. Incubate at 37 degrees C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degrees C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400  
10 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in  
15 the 96-well plate (or  $1 \times 10^5$  cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37 degrees C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the  
20 supernatant according to the protocol described in Example 17.

#### **Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.**

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes,  
25 EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or  
30 differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably

transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene  
5 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified  
10 product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30  
15 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-  
20 inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine  
25 protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80%  
30 confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

- 5        Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the  
10        supernatant according to Example 17.

#### **Example 16: High-Throughput Screening Assay for T-cell Activity**

- NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and  
15        CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

- 20        In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

- 25        Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF-KB would be useful in treating diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid  
30        arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-

KB binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5' : GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCC  
5 GGGACTTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5' : GCGGCAAGCTTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

10 PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

15 5' : CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC  
TTTCCATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTC  
CGCCCATCCCGCCCCTAACTCCGCCAGTTCGGCCCATTTCTCCGCCCCATG  
GCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTG  
AGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGC  
20 AAAAAGCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and  
25 therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the  
30 GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly,

the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### 5 **Example 17: Assay for SEAP Activity**

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

- 10 Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

- Cool the samples to room temperature for 15 minutes. Empty the dispenser  
15 and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below): Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at  
20 each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

#### **Reaction Buffer Formulation:**

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5



21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

---

**Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability**

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small

molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star  
5 black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To  
load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate  
10 is incubated at 37 degrees C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are  
re-suspended to  $2-5 \times 10^6$  cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml  
fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension.  
15 The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to  $1 \times 10^6$  cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

20 For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the  
following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4  
25 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm;  
and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an  
extracellular signaling event which has resulted in an increase in the intracellular  
Ca<sup>++</sup> concentration.

30 **Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies.

- 5 In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation  
10 of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

- 15 Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

- 20 Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or  
25 polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar  
30 Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen

Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyn plates (20,000/200ml/well) and cultured overnight in complete medium.

- 5 Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from
- 10 Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4 degrees C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on
- 15 ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degrees C at 16,000 x g.

- Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described
- 20 here.

- Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and
- 25 PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

- The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2</sub><sup>+</sup> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride,
- 30 pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the

components gently and preincubate the reaction mix at 30 degrees C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

- 5 Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degrees C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish
- 10 peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degrees C for one hour. Wash the well as above.

- Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound
- 15 peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

### **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

- 20 As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other
- 25 molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

- Specifically, assay plates are made by coating the wells of a 96-well ELISA
- 30 plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against

Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degrees C until use.

5           A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

10           After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard  
15           procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

20           **Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

            RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA  
25           is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

            PCR products are then sequenced using primers labeled at their 5' end with T4  
30           polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring

suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

#### **Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in

- 5 Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled  
10 water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

- 15 Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale).  
20 Interpolate the concentration of the polypeptide in the sample using the standard curve.

### **Example 23: Formulation**

- The invention also provides methods of treatment and/or prevention of  
25 diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type  
30 (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual



patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

5           As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for  
10 the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears  
15 to vary depending on the desired effect.

          Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid  
20 filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

          Therapeutics of the invention are also suitably administered by sustained-  
25 release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or  
30 formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials  
5 (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al.,  
10 J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990);  
15 Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP  
20 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

25 In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer  
30 (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage

injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container

having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized  
5 formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or  
10 more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in  
15 conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG  
20 (e.g., THERACYS®), MPL and nonviable preparations of *Corynebacterium parvum*. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to,  
25 Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B,  
30 whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture,

separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™

(ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott); COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'-azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of  $\beta$ -L-FD4C and  $\beta$ -L-FddC (WO 98/17281).

Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBV097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830).

Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myers Squibb); TIPRANAVIR™

(PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity  
5 against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Wellcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the  
10 HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4  
15 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists.  
20 Chemokine receptor agonists such as RANTES, SDF-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , etc., may also inhibit fusion.

Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones;  
25 ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

Additional antiretroviral agents include hydroxyurea-like compounds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide  
30 reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors such as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and  
 5 AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1 $\alpha$ , MIP-1 $\beta$ , SDF-1 $\alpha$ , IL-2, PROLEUKIN<sup>TM</sup> (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as  
 10 IFN- $\alpha$ 2a; antagonists of TNFs, NF $\kappa$ B, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune<sup>TM</sup> (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN  
 15 rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al.*, *PNAS* 94:11567-72 (1997); Chen *et al.*,  
 20 *Nat. Med.* 3:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF- $\alpha$  antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor  
 25 agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and  $\alpha$ -naphthoflavone (WO 98/30213); and antioxidants such as  $\gamma$ -L-glutamyl-L-cysteine ethyl ester ( $\gamma$ -GCE; WO 99/56764).

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered  
 30 with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.



In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™,

5 DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™,

10 LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In

15 another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™,

20 CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific

25 embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an

30 opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with

PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial  
5 infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases,  
10 Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

In other embodiments, Therapeutics of the invention are administered in  
15 combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.  
20 Other immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™,  
25 SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate mofetil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and  
30 RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™ (antithymocyte globulin), and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

10 In certain embodiments, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, 15 etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid 20 derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, 25 pifoxime, proquazone, proxazole, and tenidap.

In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life 30 Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor

of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline

analog, cis-hydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha, alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., *J. Bio. Chem.* 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., *Biochem J.* 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., *Nature* 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, *J. Clin. Invest.* 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., *J. Biol. Chem.* 262(4):1659-1664, (1987)); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., *Agents Actions* 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J. Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J. Clin. Invest.* 103:47-54 (1999)); carboxynaminimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic

inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositions of the invention include, but are not limited to, EMD-121974 (Merck KgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcosine), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouracil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C)), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone),

substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate),  
5 estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone propionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing hormone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine,  
10 estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also  
15 known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one  
20 embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or  
25 prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the  
30 invention are administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of



CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are <sup>90</sup>Y and <sup>111</sup>In.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number  
5 EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993);  
10 Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth  
15 Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent  
20 Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but  
25 are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention  
30 include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony

stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or  
5 thrombopoietin.

In certain embodiments, Therapeutics of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

10 In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amiodarone, bretylium, digitalis, digoxin, digitoxin, diltiazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

15 In another embodiment, the Therapeutics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorophenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit  $\text{Na}^+\text{-K}^+\text{-2Cl}^-$  symport (e.g., furosemide, bumetanide, azosemide, piretanide, triparamide, ethacrynic acid, 20 muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists  
25 (e.g., spironolactone, canrenone, and potassium canrenoate).

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to,  $^{127}\text{I}$ , radioactive isotopes of iodine such as  $^{131}\text{I}$  and  $^{123}\text{I}$ ; recombinant  
30 growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™

(octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T<sub>4</sub>™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T<sub>3</sub>™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca<sup>2+</sup> channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or conjugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™

(mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone),

5 LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-

10 CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™

15 (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor

20 antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotrophic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (acclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone

25 dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate),

30 CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™

(cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and

10 MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-

15 MEDROL™ and MEDROL ACETATE™ (methylprednisolone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™

20 (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™

25 (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide),

30 DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide),

DYMELOS<sup>TM</sup> (acetohexamide), glibenclamide, MICRONASE<sup>TM</sup>, DIBETA<sup>TM</sup> and GLYNASE<sup>TM</sup> (glyburide), GLUCOTROL<sup>TM</sup> (glipizide), and DIAMICRON<sup>TM</sup> (gliclazide), GLUCOPHAGE<sup>TM</sup> (metformin), PRECOSE<sup>TM</sup> (acarbose), AMARYL<sup>TM</sup> (glimepiride), and ciglitazone; thiazolidinediones (TZDs) such as rosiglitazone, AVANDIA<sup>TM</sup> (rosiglitazone maleate) ACTOS<sup>TM</sup> (pioglitazone), and troglitazone; alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN<sup>TM</sup> (octreotide); and diazoxides such as PROGLYCEM<sup>TM</sup> (diazoxide). In still other embodiments, Therapeutics of the invention are administered in combination with one or more of the following: a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent.

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN<sup>®</sup> and ESTRATAB<sup>®</sup>), estradiols (e.g., CLIMARA<sup>®</sup> and ALORA<sup>®</sup>), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN<sup>®</sup> (medroxyprogesterone), MICRONOR<sup>®</sup> (norethidrone acetate), PROMETRIUM<sup>®</sup> progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example, conjugated estrogens/medroxyprogesterone (e.g., PREMPRO<sup>TM</sup> and PREMPHASE<sup>®</sup>) and norethindrone acetate/ethinyl estradiol (e.g., FEMHRT<sup>TM</sup>).

In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL<sup>TM</sup>), ferrous fumarate (e.g., FEOSTAT<sup>TM</sup>), ferrous gluconate (e.g., FERGON<sup>TM</sup>), polysaccharide-iron complex (e.g., NIFEREX<sup>TM</sup>), iron dextran injection (e.g., INFED<sup>TM</sup>), cupric sulfate, pyroxidine, riboflavin, Vitamin B<sub>12</sub>, cyanocobalamin injection (e.g., REDISOL<sup>TM</sup>, RUBRAMIN PC<sup>TM</sup>), hydroxocobalamin, folic acid (e.g., FOLVITE<sup>TM</sup>), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

In certain embodiments, the Therapeutics of the invention are administered in combination with agents used to treat psychiatric disorders. Psychiatric drugs that may be administered with the Therapeutics of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine, divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranlycypromine, trazodone, trimipramine, and venlafaxine), antianxiety agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d-amphetamine, methylphenidate, and pemoline).

In other embodiments, the Therapeutics of the invention are administered in combination with agents used to treat neurological disorders. Neurological agents that may be administered with the Therapeutics of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g., levodopa/carbidopa, selegiline, amantidine, bromocriptine, pergolide, ropinirole, pramipexole, benzotropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, tolcapone), and ALS therapeutics (e.g. riluzole).

In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril,trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and



nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

- 5           In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

**Example 24: Method of Treating Decreased Levels of the Polypeptide**

- 10           The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in  
15           the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the polypeptide to  
20           increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

25

**Example 25: Method of Treating Increased Levels of the Polypeptide**

- The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically  
30           effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

#### 10 **Example 26: Method of Treatment Using Gene Therapy-Ex Vivo**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine

sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto  
5 agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the  
10 gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media,  
15 containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no  
20 selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or  
25 after having been grown to confluence on cytodex 3 microcarrier beads.

#### **Example 27: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention**

Another method of gene therapy according to the present invention involves  
30 operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411,

published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in  
5 the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be  
10 operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second  
15 targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added  
20 together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

In this Example, the polynucleotide constructs are administered as naked  
25 polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place  
30 which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the

polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary  
5 phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na<sub>2</sub> HPO<sub>4</sub>, 6 mM dextrose). The cells are recentrifuged, the  
10 supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately  $3 \times 10^6$  cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to  
15 construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an  
20 Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-  
25 digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120  $\mu$ g/ml. 0.5 ml of the cell suspension (containing approximately  $1.5 \times 10^6$  cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is  
30 performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960  $\mu$ F and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their

genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer  
5 pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after  
10 having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

#### **Example 28: Method of Treatment Using Gene Therapy - In Vivo**

15 Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter  
20 or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318  
25 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The  
30 polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are

free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in

5 Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain

10 sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to

15 provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and

20 connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of

25 the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely

30 differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after



preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

5

**Example 29: Transgenic Animals.**

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*,  
10 baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e.,  
15 polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus  
20 mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science  
25 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

30 Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to

quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate  
5 lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to  
10 produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of  
15 polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

### **Example 30: Knock-Out Animals.**

20 Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional  
25 polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in  
30 the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in

research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly  
5 administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are  
10 administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the  
15 invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors; and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.  
20 The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or  
25 intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and  
30 Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing  
5 for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or  
10 conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

### **Example 31: Production of an Antibody**

#### **Hybridoma Technology**

15 The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide(s) of the invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide(s) of the invention is prepared and purified to render it  
20 substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide(s) of the invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976);  
25 Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide(s) of the invention, or, more preferably, with a secreted polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with  
30 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are  
5 selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide(s) of the invention.

Alternatively, additional antibodies capable of binding polypeptide(s) of the  
10 invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to  
15 produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide(s) of the invention protein-specific antibody can be blocked by polypeptide(s) of the invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide(s) of the invention protein-specific antibody and are used to immunize an animal to induce  
20 formation of further polypeptide(s) of the invention protein-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein.  
25 (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

30

*Isolation Of Antibody Fragments Directed polypeptide(s) of the invention From A Library Of scFvs*

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide(s) of the invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

5       Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10<sup>9</sup> E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture  
10 is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10<sup>8</sup> TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml  
15 kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III  
20 particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-  
25 AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10<sup>13</sup> transducing units/ml (ampicillin-resistant clones).

30       Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times

in PBS. Approximately 10<sup>13</sup> TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

### **Example 32: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation**

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been



found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

- 5           One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in
- 10           determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

- In Vitro Assay- Purified polypeptides of the invention, or truncated forms
- 15           thereof, is assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the polypeptides of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in
- 20           the presence of either formalin-fixed Staphylococcus aureus Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B
- 25           cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

- Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added  $10^5$  B-cells suspended in culture medium (RPMI 1640 containing 10% FBS,  $5 \times 10^{-5}$  M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and  $10^{-5}$  dilution of
- 30           SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with  $^3$ H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of a polypeptide of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with polypeptides of the invention identify the results of the activity of the polypeptides on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with polypeptide is used to indicate whether the polypeptide specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and polypeptide-treated mice.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

### Example 33: T Cell Proliferation Assay

#### **Proliferation assay for Resting PBLs.**

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of  $^3\text{H}$ -thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 microliters per well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4°C (1 microgram/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells ( $5 \times 10^4$ /well) of mAb coated plates in RPMI containing

10% FCS and P/S in the presence of varying concentrations of TNF Delta and/or TNF Epsilon protein (total volume 200 microliters). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37°C, plates are spun for 2 min. at 1000 rpm and 100 microliters of supernatant is removed and stored -20°C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 microliters of medium containing 0.5 microcuries of <sup>3</sup>H-thymidine and cultured at 37°C for 18-24 hr. Wells are harvested and incorporation of <sup>3</sup>H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of TNF Delta and/or TNF Epsilon proteins.

Alternatively, a proliferation assay on resting PBL (peripheral blood lymphocytes) is measured by the up-take of <sup>3</sup>H-thymidine. The assay is performed as follows. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non-adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2 x 10<sup>4</sup> cells/well in a final volume of 200 microliters. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2 (\*), IFN $\gamma$ , TNF $\alpha$ , IL-10 and TR2. In addition to the control supernatants, recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 100ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of <sup>3</sup>H-thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of <sup>3</sup>H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

(\*) The amount of the control cytokines IL-2, IFN $\gamma$ , TNF $\alpha$  and IL-10 produced in each transfection varies between 300pg to 5ng/ml.

#### **Costimulation assay.**

5        A costimulation assay on resting PBL (peripheral blood lymphocytes) is performed in the presence of immobilized antibodies to CD3 and CD28. The use of antibodies specific for the invariant regions of CD3 mimic the induction of T cell activation that would occur through stimulation of the T cell receptor by an antigen. Cross-linking of the TCR (first signal) in the absence of a costimulatory signal  
10 (second signal) causes very low induction of proliferation and will eventually result in a state of "anergy", which is characterized by the absence of growth and inability to produce cytokines. The addition of a costimulatory signal such as an antibody to CD28, which mimics the action of the costimulatory molecule. B7-1 expressed on activated APCs, results in enhancement of T cell responses including cell survival and  
15 production of IL-2. Therefore this type of assay allows to detect both positive and negative effects caused by addition of supernatants expressing the proteins of interest on T cell proliferation.

      The assay is performed as follows. Ninety-six well plates are coated with 100ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final  
20 volume of 100ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to  
25 attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using  $2 \times 10^4$  cells/well in a final volume of 200ul. The supernatants (e.g., CHO or 293T  
30 supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins:

vector only (negative control), IL-2, IFN $\gamma$ , TNF $\alpha$ , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of  $^3\text{H}$ -thymidine (Nen, Boston, MA). Cells are then harvested 20  
5 hours following pulsing and incorporation of  $^3\text{H}$ -thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

**Costimulation assay: IFN  $\gamma$  and IL-2 ELISA.**

10 The assay is performed as follows. Twenty-four well plates are coated with either 300ng/ml or 600ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 500ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood,  
15 and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are  
20 collected, washed and used in the costimulation assay. The assay is performed in the pre-coated twenty-four well plate using  $1 \times 10^5$  cells/well in a final volume of 900ul. The supernatants (293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 300ul are added to 600ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the  
25 following proteins: vector only(negative control), IL-2, IFN $\gamma$ , IL-12 and IL-18. In addition to the control supernatants recombinant human IL-2 (all cytokines were purchased from R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml, IL-12 at a final concentration of 1ng/ml and IL-18 at a final concentration of 50ng/ml are also used. Controls and unknown samples are tested in duplicate.  
30 Supernatant samples (250ul) are collected 2 days and 5 days after the beginning of the assay. ELISAs to test for IFN $\gamma$  and IL-2 secretion are performed using kits

purchased from R & D Systems, (Minneapolis, MN). Results are expressed as an average of duplicate samples plus or minus standard error.

#### **Proliferation assay for preactivated-resting T cells.**

5           A proliferation assay on preactivated-resting T cells is performed on cells that are previously activated with the lectin phytohemagglutinin (PHA). Lectins are polymeric plant proteins that can bind to residues on T cell surface glycoproteins including the TCR and act as polyclonal activators. PBLs treated with PHA and then cultured in the presence of low doses of IL-2 resemble effector T cells. These cells  
10   are generally more sensitive to further activation induced by growth factors such as IL-2. This is due to the expression of high affinity IL-2 receptors that allows this population to respond to amounts of IL-2 that are 100 fold lower than what would have an effect on a naïve T cell. Therefore the use of this type of cells might enable to detect the effect of very low doses of an unknown growth factor, that would not be  
15   sufficient to induce proliferation on resting (naïve ) T cells.

          The assay is performed as follows. PBMC are isolated by F/H gradient centrifugation from human peripheral blood, and are cultured in 10% FCS (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD) in the presence of 2 µg/ml PHA (Sigma, Saint Louis, MO) for three days. The cells are then  
20   washed in PBS and cultured in 10% FCS/RPMI in the presence of 5 ng/ml of human recombinant IL-2 (R & D Systems, Minneapolis, MN) for 3 days. The cells are washed and rested in starvation medium (1% FCS/RPMI) for 16 hours prior to the beginning of the proliferation assay. An aliquot of the cells is analyzed by FACS to determine the percentage of T cells (CD3 positive cells) present; this usually ranges  
25   between 93-97% depending on the donor. The assay is performed in a 96 well plate using  $2 \times 10^4$  cells/well in a final volume of 200 µl. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60 µl are added to 140 µl of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins:  
30   vector (negative control), IL-2, IFN $\gamma$ , TNF $\alpha$ , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 at a final concentration of 10 ng/ml is also used. After 24 hours of culture, each well is pulsed with 1 µCi of  $^3\text{H}$ -

thymidine(Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of  $^3\text{H}$ -thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

The studies described in this example test activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

**Example 34: Effect of Polypeptides of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells**

Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- $\alpha$ , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC $\gamma$ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to

measure the IL-12 release as follows. Dendritic cells ( $10^6/\text{ml}$ ) are treated with increasing concentrations of polypeptides of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Polypeptides, agonists, or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.



Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of  $2 \times 10^6$ /ml in PBS containing PI at a final concentration of 5  $\mu$ g/ml, and then incubated at room temperature for 5 minutes before FACSscan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of  $5 \times 10^5$  cells/ml with increasing concentrations of the a polypeptide of the invention and under the same conditions, but in the absence of the polypeptide. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of a polypeptide of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g., R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

Oxidative burst. Purified monocytes are plated in 96-w plate at  $2 \times 10^5$  cell/well. Increasing concentrations of polypeptides of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM

dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20  $\mu$ l 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H<sub>2</sub>O<sub>2</sub> produced by the macrophages, a standard curve of a H<sub>2</sub>O<sub>2</sub> solution of known molarity is performed for each experiment.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polypeptides, polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

### **Example 35: Biological Effects of Polypeptides of the Invention**

#### **Astrocyte and Neuronal Assays**

Recombinant polypeptides of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate a polypeptide of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of a polypeptide of the invention to

induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

#### Fibroblast and endothelial cell assays

5 Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated  
10 for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE<sub>2</sub> assays, the human lung fibroblasts are cultured at  
15 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or polypeptides of the invention with or without IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for PGE<sub>2</sub> by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are  
20 cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without polypeptides of the invention IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or polypeptides of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth  
25 of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with polypeptides of the invention.

#### Parkinson Models.

30 The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic

projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP<sup>+</sup>) and released.

5 Subsequently, MPP<sup>+</sup> is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP<sup>+</sup> is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

10 It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J.  
15 Neuroscience, 1990).

Based on the data with FGF-2, polypeptides of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential  
20 effect of a polypeptide of the invention is first examined *in vitro* in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm<sup>2</sup> on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium  
25 containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

30 Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons

would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if a polypeptide of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the polypeptide may be involved in Parkinson's Disease.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### **Example 36: The Effect of Polypeptides of the Invention on the Growth of Vascular Endothelial Cells**

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at  $2-5 \times 10^4$  cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. A polypeptide having the amino acid sequence of SEQ ID NO:Y, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the polypeptide of the invention may proliferate vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### **Example 37: Stimulatory Effect of Polypeptides of the Invention on the Proliferation of Vascular Endothelial Cells**

For evaluation of mitogenic activity of growth factors, the colorimetric MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)2H-tetrazolium) assay with the electron coupling reagent PMS (phenazine methosulfate) was

performed (CellTiter 96 AQ, Promega). Cells are seeded in a 96-well plate (5,000 cells/well) in 0.1 mL serum-supplemented medium and are allowed to attach overnight. After serum-starvation for 12 hours in 0.5% FBS, conditions (bFGF, VEGF<sub>165</sub> or a polypeptide of the invention in 0.5% FBS) with or without Heparin (8 U/ml) are added to wells for 48 hours. 20 mg of MTS/PMS mixture (1:0.05) are added per well and allowed to incubate for 1 hour at 37°C before measuring the absorbance at 490 nm in an ELISA plate reader. Background absorbance from control wells (some media, no cells) is subtracted, and seven wells are performed in parallel for each condition. See, Leak *et al. In Vitro Cell. Dev. Biol.* 30A:512-518 (1994).

10       The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

15       **Example 38: Inhibition of PDGF-induced Vascular Smooth Muscle Cell Proliferation Stimulatory Effect**

HAoSMC proliferation can be measured, for example, by BrdUrd incorporation. Briefly, subconfluent, quiescent cells grown on the 4-chamber slides are transfected with CRP or FITC-labeled AT2-3LP. Then, the cells are pulsed with 10% calf serum and 6 mg/ml BrdUrd. After 24 h, immunocytochemistry is performed by using BrdUrd Staining Kit (Zymed Laboratories). In brief, the cells are incubated with the biotinylated mouse anti-BrdUrd antibody at 4 degrees C for 2 h after being exposed to denaturing solution and then incubated with the streptavidin-peroxidase and diaminobenzidine. After counterstaining with hematoxylin, the cells are mounted for microscopic examination, and the BrdUrd-positive cells are counted. The BrdUrd index is calculated as a percent of the BrdUrd-positive cells to the total cell number. In addition, the simultaneous detection of the BrdUrd staining (nucleus) and the FITC uptake (cytoplasm) is performed for individual cells by the concomitant use of bright field illumination and dark field-UV fluorescent illumination. See, Hayashida et al., *J. Biol. Chem.* 6:271(36):21985-21992 (1996).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

### **Example 39: Stimulation of Endothelial Migration**

This example will be used to explore the possibility that a polypeptide of the invention may stimulate lymphatic endothelial cell migration.

10        Endothelial cell migration assays are performed using a 48 well microchemotaxis chamber (Neuroprobe Inc., Cabin John, MD; Falk, W., et al., J. Immunological Methods 1980;33:239-247). Polyvinylpyrrolidone-free polycarbonate filters with a pore size of 8 um (Nucleopore Corp. Cambridge, MA) are coated with 0.1% gelatin for at least 6 hours at room temperature and dried under sterile air. Test substances are diluted to appropriate  
15        concentrations in M199 supplemented with 0.25% bovine serum albumin (BSA), and 25 ul of the final dilution is placed in the lower chamber of the modified Boyden apparatus. Subconfluent, early passage (2-6) HUVEC or BMEC cultures are washed and trypsinized for the minimum time required to achieve cell detachment. After placing the filter between lower and upper chamber,  $2.5 \times 10^5$  cells suspended in 50 ul M199 containing 1%  
20        FBS are seeded in the upper compartment. The apparatus is then incubated for 5 hours at 37°C in a humidified chamber with 5% CO<sub>2</sub> to allow cell migration. After the incubation period, the filter is removed and the upper side of the filter with the non-migrated cells is scraped with a rubber policeman. The filters are fixed with methanol and stained with a Giemsa solution (Diff-Quick, Baxter, McGraw Park, IL). Migration is quantified by  
25        counting cells of three random high-power fields (40x) in each well, and all groups are performed in quadruplicate.

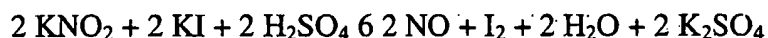
30        The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 40: Stimulation of Nitric Oxide Production by Endothelial Cells**

Nitric oxide released by the vascular endothelium is believed to be a mediator of vascular endothelium relaxation. Thus, activity of a polypeptide of the invention can be  
 5 assayed by determining nitric oxide production by endothelial cells in response to the polypeptide.

Nitric oxide is measured in 96-well plates of confluent microvascular endothelial cells after 24 hours starvation and a subsequent 4 hr exposure to various levels of a positive control (such as VEGF-1) and the polypeptide of the invention. Nitric oxide in  
 10 the medium is determined by use of the Griess reagent to measure total nitrite after reduction of nitric oxide-derived nitrate by nitrate reductase. The effect of the polypeptide of the invention on nitric oxide release is examined on HUVEC.

Briefly, NO release from cultured HUVEC monolayer is measured with a NO-specific polarographic electrode connected to a NO meter (Iso-NO, World Precision  
 15 Instruments Inc.) (1049). Calibration of the NO elements is performed according to the following equation:



The standard calibration curve is obtained by adding graded concentrations of  $\text{KNO}_2$  (0, 5, 10, 25, 50, 100, 250, and 500 nmol/L) into the calibration solution containing  
 20 KI and  $\text{H}_2\text{SO}_4$ . The specificity of the Iso-NO electrode to NO is previously determined by measurement of NO from authentic NO gas (1050). The culture medium is removed and HUVECs are washed twice with Dulbecco's phosphate buffered saline. The cells are then bathed in 5 ml of filtered Krebs-Henseleit solution in 6-well plates, and the cell plates are kept on a slide warmer (Lab Line Instruments Inc.) To maintain the temperature at 37°C.  
 25 The NO sensor probe is inserted vertically into the wells, keeping the tip of the electrode 2 mm under the surface of the solution, before addition of the different conditions. S-nitroso acetyl penicillamin (SNAP) is used as a positive control. The amount of released NO is expressed as picomoles per  $1 \times 10^6$  endothelial cells. All values reported are means of four to six measurements in each group (number of cell culture wells). See,  
 30 Leak *et al. Biochem. and Biophys. Res. Comm.* 217:96-105 (1995).

The studies described in this example tested activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to



test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 41: Effect of Polypeptides of the Invention on Cord Formation in**

**Angiogenesis**

Another step in angiogenesis is cord formation, marked by differentiation of endothelial cells. This bioassay measures the ability of microvascular endothelial cells to form capillary-like structures (hollow structures) when cultured *in vitro*.

10 CADMEC (microvascular endothelial cells) are purchased from Cell Applications, Inc. as proliferating (passage 2) cells and are cultured in Cell Applications' CADMEC Growth Medium and used at passage 5. For the *in vitro* angiogenesis assay, the wells of a 48-well cell culture plate are coated with Cell Applications' Attachment Factor Medium (200 µl/well) for 30 min. at 37°C. CADMEC are seeded onto the coated wells at 7,500  
15 cells/well and cultured overnight in Growth Medium. The Growth Medium is then replaced with 300 µg Cell Applications' Chord Formation Medium containing control buffer or a polypeptide of the invention (0.1 to 100 ng/ml) and the cells are cultured for an additional 48 hr. The numbers and lengths of the capillary-like chords are quantitated through use of the Boeckeler VIA-170 video image analyzer. All assays are done in  
20 triplicate.

Commercial (R&D) VEGF (50 ng/ml) is used as a positive control. b-esteradiol (1 ng/ml) is used as a negative control. The appropriate buffer (without protein) is also utilized as a control.

The studies described in this example tested activity of a polypeptide of the  
25 invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 42: Angiogenic Effect on Chick Chorioallantoic Membrane**

30

Chick chorioallantoic membrane (CAM) is a well-established system to examine angiogenesis. Blood vessel formation on CAM is easily visible and quantifiable. The

ability of polypeptides of the invention to stimulate angiogenesis in CAM can be examined.

Fertilized eggs of the White Leghorn chick (*Gallus gallus*) and the Japanese quail (*Coturnix coturnix*) are incubated at 37.8°C and 80% humidity. Differentiated CAM of  
5 16-day-old chick and 13-day-old quail embryos is studied with the following methods.

On Day 4 of development, a window is made into the egg shell of chick eggs. The embryos are checked for normal development and the eggs sealed with cellotape. They are further incubated until Day 13. Thermanox coverslips (Nunc, Naperville, IL) are cut into disks of about 5 mm in diameter. Sterile and salt-free growth factors are dissolved in  
10 distilled water and about 3.3 mg/ 5 ml are pipetted on the disks. After air-drying, the inverted disks are applied on CAM. After 3 days, the specimens are fixed in 3% glutaraldehyde and 2% formaldehyde and rinsed in 0.12 M sodium cacodylate buffer. They are photographed with a stereo microscope [Wild M8] and embedded for semi- and ultrathin sectioning as described above. Controls are performed with carrier disks alone.

15 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### 20 **Example 43: Angiogenesis Assay Using a Matrigel Implant in Mouse**

*In vivo* angiogenesis assay of a polypeptide of the invention measures the ability of an existing capillary network to form new vessels in an implanted capsule of murine extracellular matrix material (Matrigel). The protein is mixed with the liquid Matrigel at 4  
25 degree C and the mixture is then injected subcutaneously in mice where it solidifies. After 7 days, the solid "plug" of Matrigel is removed and examined for the presence of new blood vessels. Matrigel is purchased from Becton Dickinson Labware/Collaborative Biomedical Products.

When thawed at 4 degree C the Matrigel material is a liquid. The Matrigel is  
30 mixed with a polypeptide of the invention at 150 ng/ml at 4 degrees C and drawn into cold 3 ml syringes. Female C57Bl/6 mice approximately 8 weeks old are injected with the

mixture of Matrigel and experimental protein at 2 sites at the midventral aspect of the abdomen (0.5 ml/site). After 7 days, the mice are sacrificed by cervical dislocation, the Matrigel plugs are removed and cleaned (i.e., all clinging membranes and fibrous tissue is removed). Replicate whole plugs are fixed in neutral buffered 10% formaldehyde, embedded in paraffin and used to produce sections for histological examination after staining with Masson's Trichrome. Cross sections from 3 different regions of each plug are processed. Selected sections are stained for the presence of vWF. The positive control for this assay is bovine basic FGF (150 ng/ml). Matrigel alone is used to determine basal levels of angiogenesis.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### **Example 44: Rescue of Ischemia in Rabbit Lower Limb Model**

To study the in vivo effects of polynucleotides and polypeptides of the invention on ischemia, a rabbit hindlimb ischemia model is created by surgical removal of one femoral arteries as described previously (Takeshita *et al.*, *Am J. Pathol* 147:1649-1660 (1995)). The excision of the femoral artery results in retrograde propagation of thrombus and occlusion of the external iliac artery. Consequently, blood flow to the ischemic limb is dependent upon collateral vessels originating from the internal iliac artery (Takeshita *et al.* *Am J. Pathol* 147:1649-1660 (1995)). An interval of 10 days is allowed for post-operative recovery of rabbits and development of endogenous collateral vessels. At 10 day post-operatively (day 0), after performing a baseline angiogram, the internal iliac artery of the ischemic limb is transfected with 500 mg naked expression plasmid containing a polynucleotide of the invention by arterial gene transfer technology using a hydrogel-coated balloon catheter as described (Riessen *et al.* *Hum Gene Ther.* 4:749-758 (1993); Leclerc *et al.* *J. Clin. Invest.* 90: 936-944 (1992)). When a polypeptide of the invention is used in the treatment, a single bolus of 500 mg polypeptide of the invention or control is delivered into the internal iliac artery of the ischemic limb over a period of 1

min. through an infusion catheter. On day 30, various parameters are measured in these rabbits: (a) BP ratio - The blood pressure ratio of systolic pressure of the ischemic limb to that of normal limb; (b) Blood Flow and Flow Reserve - Resting FL: the blood flow during undilated condition and Max FL: the blood flow during fully dilated condition (also an indirect measure of the blood vessel amount) and Flow Reserve is reflected by the ratio of max FL: resting FL; (c) Angiographic Score - This is measured by the angiogram of collateral vessels. A score is determined by the percentage of circles in an overlaying grid that with crossing opacified arteries divided by the total number in the rabbit thigh; (d) Capillary density - The number of collateral capillaries determined in light microscopic sections taken from hindlimbs.

The studies described in this example tested activity of polynucleotides and polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the agonists, and/or antagonists of the invention.

#### **Example 45: Effect of Polypeptides of the Invention on Vasodilation**

Since dilation of vascular endothelium is important in reducing blood pressure, the ability of polypeptides of the invention to affect the blood pressure in spontaneously hypertensive rats (SHR) is examined. Increasing doses (0, 10, 30, 100, 300, and 900 mg/kg) of the polypeptides of the invention are administered to 13-14 week old spontaneously hypertensive rats (SHR). Data are expressed as the mean  $\pm$  SEM. Statistical analysis are performed with a paired t-test and statistical significance is defined as  $p < 0.05$  vs. the response to buffer alone.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### **Example 46: Rat Ischemic Skin Flap Model**

The evaluation parameters include skin blood flow, skin temperature, and factor VIII immunohistochemistry or endothelial alkaline phosphatase reaction. Expression of

polypeptides of the invention, during the skin ischemia, is studied using in situ hybridization.

The study in this model is divided into three parts as follows:

Ischemic skin

5 Ischemic skin wounds

Normal wounds

The experimental protocol includes:

Raising a 3x4 cm, single pedicle full-thickness random skin flap (myocutaneous flap over the lower back of the animal).

10 An excisional wounding (4-6 mm in diameter) in the ischemic skin (skin-flap).

Topical treatment with a polypeptide of the invention of the excisional wounds (day 0, 1, 2, 3, 4 post-wounding) at the following various dosage ranges: 1mg to 100 mg.

Harvesting the wound tissues at day 3, 5, 7, 10, 14 and 21 post-wounding for histological, immunohistochemical, and in situ studies.

15 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

#### 20 **Example 47: Peripheral Arterial Disease Model**

Angiogenic therapy using a polypeptide of the invention is a novel therapeutic strategy to obtain restoration of blood flow around the ischemia in case of peripheral arterial diseases. The experimental protocol includes:

25 One side of the femoral artery is ligated to create ischemic muscle of the hindlimb, the other side of hindlimb serves as a control.

A polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-3 weeks.

30 The ischemic muscle tissue is collected after ligation of the femoral artery at 1, 2, and 3 weeks for the analysis of expression of a polypeptide of the invention and histology. Biopsy is also performed on the other side of normal muscle of the contralateral hindlimb.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

**Example 48: Ischemic Myocardial Disease Model**

A polypeptide of the invention is evaluated as a potent mitogen capable of stimulating the development of collateral vessels, and restructuring new vessels after coronary artery occlusion. Alteration of expression of the polypeptide is investigated in situ. The experimental protocol includes:

The heart is exposed through a left-side thoracotomy in the rat. Immediately, the left coronary artery is occluded with a thin suture (6-0) and the thorax is closed.

A polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-4 weeks.

Thirty days after the surgery, the heart is removed and cross-sectioned for morphometric and in situ analyzes.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 49: Rat Corneal Wound Healing Model**

This animal model shows the effect of a polypeptide of the invention on neovascularization. The experimental protocol includes:

Making a 1-1.5 mm long incision from the center of cornea into the stromal layer. Inserting a spatula below the lip of the incision facing the outer corner of the eye. Making a pocket (its base is 1-1.5 mm from the edge of the eye). Positioning a pellet, containing 50ng- 5ug of a polypeptide of the invention, within the pocket.

Treatment with a polypeptide of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

### **Example 50: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models**

#### ***Diabetic db+/db+ Mouse Model.***

10 To demonstrate that a polypeptide of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than  
15 contraction (Gartner, M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single  
20 autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al. Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am.*  
25 *J. of Pathol.* 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*, *Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These  
30 homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic  
5 (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional  
10 Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01  
15 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The  
20 wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily  
25 measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

A polypeptide of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups  
30 received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for



histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

5        Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

10

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung  
15        microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with a polypeptide of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-  
20        epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte  
25        growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer can serve as a positive tissue control and human brain tissue can be used as a  
30        negative tissue control. Each specimen includes a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is

based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

5

### ***Steroid Impaired Rat Model***

The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)).

10

Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *Am. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

15

20

25

To demonstrate that a polypeptide of the invention can accelerate the healing process, the effects of multiple topical applications of the polypeptide on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

30

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is

conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of  
5 wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the  
10 testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement  
15 on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The polypeptide of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups  
20 received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

25 Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing  
30 the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are  
5 sectioned perpendicular to the wound surface (5mm) and cut using an Olympus  
microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of  
bisected wounds. Histologic examination of the wounds allows assessment of whether the  
healing process and the morphologic appearance of the repaired skin is improved by  
treatment with a polypeptide of the invention. A calibrated lens micrometer is used by a  
10 blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is  
considered significant.

The studies described in this example tested activity of a polypeptide of the  
invention. However, one skilled in the art could easily modify the exemplified studies to  
15 test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the  
invention.

### **Example 51: Lymphadema Animal Model**

20 The purpose of this experimental approach is to create an appropriate and  
consistent lymphedema model for testing the therapeutic effects of a polypeptide of the  
invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system  
in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb,  
quantification of the amount of lymphatic vasculature, total blood plasma protein, and  
25 histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly,  
the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration  
analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital.  
Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed  
30 with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing.  
Circumference and volumetric measurements are made prior to injecting dye into paws  
after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The

intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

- Using the knee joint as a landmark, a mid-leg inguinal incision is made
- 5 circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated suture ligated.

- Using a microscope, muscles in back of the leg (near the semitendinosus and
- 10 adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

- Care is taken to control any mild bleeding resulting from this procedure. After
- 15 lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

- To avoid infection, animals are housed individually with mesh (no bedding).
- 20 Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing
- 25 perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

- Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged.
- 30 Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under

brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the  
5 limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and  $\text{Ca}^{2+}$  comparison.

Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control  
10 legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon  
15 sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the  
20 invention.

**Example 52: Suppression of TNF alpha-induced adhesion molecule expression by a Polypeptide of the Invention**

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules  
25 (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium  
30 determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The

local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Tumor necrosis factor alpha (TNF- $\alpha$ ), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of a polypeptide of the invention to mediate a suppression of TNF- $\alpha$  induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF- $\alpha$  treated ECs when co-stimulated with a member of the FGF family of proteins.

To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO<sub>2</sub>.

HUVECs are seeded in 96-well plates at concentrations of  $1 \times 10^4$  cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90  $\mu$ l of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10  $\mu$ l volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with Ca<sup>++</sup> and Mg<sup>++</sup>) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10  $\mu$ l of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20  $\mu$ l of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100  $\mu$ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 ( $10^0$ ) >  $10^{-0.5}$  >  $10^{-1}$  >  $10^{-1.5}$ . 5  $\mu$ l of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100  $\mu$ l of pNPP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50  $\mu$ l of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

### **Example 53: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation**

This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor



exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or  
5 agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL-3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells  
10 are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to  $2.5 \times 10^5$  cells/ml. During this time, 100  $\mu$ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that  
15 can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10  $\mu$ l of prepared cytokines, 50  $\mu$ l SID (supernatants at 1:2 dilution = 50  $\mu$ l) and 20  $\mu$ l of diluted cells are added to the media which is already present in the wells to  
20 allow for a final total volume of 100  $\mu$ l. The plates are then placed in a 37°C/5% CO<sub>2</sub> incubator for five days.

Eighteen hours before the assay is harvested, 0.5  $\mu$ Ci/well of [3H] Thymidine is added in a 10  $\mu$ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat  
25 using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60  $\mu$ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined  
30 via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

5 As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of  
10 cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the “Immune Activity” and  
15 “Infectious Disease” sections above, and elsewhere herein.

#### **Example 54: Assay for Extracellular Matrix Enhanced Cell Response (EMECCR)**

The objective of the Extracellular Matrix Enhanced Cell Response (EMECCR) assay is to identify gene products (e.g., isolated polypeptides) that act on the  
20 hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM.  
25 Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the  $\alpha_5\beta_1$  and  $\alpha_4\beta_1$  integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The  
30 factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of  $0.2 \mu\text{g}/\text{cm}^2$ . Mouse bone marrow cells are plated (1,000 cells/well ) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 ( 5 ng/ml ) + SCF ( 50 ng/ml ) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment ( 5%  $\text{CO}_2$ , 7%  $\text{O}_2$ , and 88%  $\text{N}_2$  ) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

If a particular gene product is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

#### **Example 55: Human Dermal Fibroblast and Aortic Smooth Muscle Cell**

##### **Proliferation**

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF $\alpha$  stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100  $\mu$ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5  $\mu$ g/ml hEGF, 5mg/ml insulin, 1 $\mu$ g/ml hFGF, 50mg/ml gentamycin, 50  $\mu$ g/ml Amphotericin B, 5%FBS. After incubation @ 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50 $\mu$ g/ml Amphotericin B, 0.4% FBS. Incubate at 37C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed which should always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNF $\alpha$  is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Then add 1/3 vol media containing controls or supernatants and incubate at 37C/5% CO<sub>2</sub> until day 5.

Transfer 60 $\mu$ l from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4C until Day 6 (for IL6 ELISA). To the remaining 100  $\mu$ l in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10 $\mu$ l). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100  $\mu$ l/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200  $\mu$ l/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50  $\mu$ l/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

Wash plates with wash buffer and blot on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100  $\mu$ l/well. Cover the plate and incubate 1 h at RT. Wash plates with wash buffer. Blot on paper towels.

Add 100  $\mu$ l/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay were tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the gene product of interest may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the gene/gene product

of interest. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the gene product and polynucleotides of the gene may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

**Example 56: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells**

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100  $\mu$ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10  $\mu$ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10  $\mu$ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20  $\mu$ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100  $\mu$ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 ( $10^0$ ) >  $10^{-0.5}$  >  $10^{-1}$  >  $10^{-1.5}$ . 5  $\mu$ l of each dilution is added to triplicate wells and the resulting AP content in

each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100  $\mu$ l of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50  $\mu$ l of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

#### **Example 57: Alamar Blue Endothelial Cells Proliferation Assay**

10 This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue  
15 Proliferation Assay is prepared in EGM-2MV with 10 ng/ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and  
20 Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37°C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of  
25 interest or control protein sample(s) (prepared in SFM ) in triplicate wells with additional bFGF to a concentration of 10 ng/ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37°C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The  
30 plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.



Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

#### **Example 58: Detection of Inhibition of a Mixed Lymphocyte Reaction**

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM<sup>®</sup>, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to  $2 \times 10^6$  cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY)

supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to  $2 \times 10^5$  cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50  $\mu$ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1  $\mu$ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10  $\mu$ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO<sub>2</sub>, and 1  $\mu$ C of [<sup>3</sup>H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. Additionally, the specifications and sequence listings of U.S. Provisional Application Nos. 60/270,658 and 60/304,444, filed February 23, 2001 and July 12, 2001, respectively, are hereby incorporated by reference in its entirety.

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 95, Table 1A.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit

February 23, 2001

Accession Number

PTA-3101

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

	For receiving Office use only			For International Bureau use only	
<input type="checkbox"/> This sheet was received with the international application			<input type="checkbox"/> This sheet was received by the International Bureau on:		
Authorized officer			Authorized officer		

**ATCC Deposit No. PTA-3101****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**ATCC Deposit No.: PTA-3101****UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 99 Table 1A.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit

February 23, 2001

Accession Number

PTA-3102

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

	For receiving Office use only			For International Bureau use only	
<input type="checkbox"/> This sheet was received with the international application			<input type="checkbox"/> This sheet was received by the International Bureau on:		
Authorized officer			Authorized officer		

**ATCC Deposit No. PTA-3102****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**ATCC Deposit No.: PTA-3102****UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

**A.** The indications made below relate to the deposited microorganism or other biological material referred to in the description on Page 95 Table 1A.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit

February 23, 2001

Accession Number

PTA-3103

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

The indications listed below will be submitted to the international Bureau later (*specify the general nature of the indications e.g., "Accession Number of Deposit"*)

	For receiving Office use only			For International Bureau use only	
<input type="checkbox"/> This sheet was received with the international application			<input type="checkbox"/> This sheet was received by the International Bureau on:		
Authorized officer			Authorized officer		

**ATCC Deposit No. PTA-3103****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**ATCC Deposit No.: PTA-3103**

## **UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

## **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

## **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

## **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

***What Is Claimed Is:***

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group  
5 consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

10 (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

15 (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID  
20 NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

25 (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

5           3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

10           4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

15           5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

20           6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

25           7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

            8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

30           9. A recombinant host cell produced by the method of claim 8.

            10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

5 (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

10 (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

15 (g) a variant of SEQ ID NO:Y;

(h) an allelic variant of SEQ ID NO:Y; or

(i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

25 14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

30 (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount  
5 of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or absence of a mutation in the  
10 polynucleotide of claim 1; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to  
15 a pathological condition in a subject comprising:

- (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the  
20 polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

- (a) contacting the polypeptide of claim 11 with a binding partner; and
- 25 (b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

30 22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;

- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

5            23.    The product produced by the method of claim 20.



<110> Human Genome Sciences, Inc.

<120> 83 Human Secreted Proteins

<130> PS735PCT

<150> 60/270,658

<151> 2001-02-23

<150> 60/304,444

<151> 2001-07-12

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&lt;213&gt; Homo sapiens

&lt;400&gt; 14

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 <212> DNA  
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 <212> DNA  
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 <212> DNA  
 <213> Homo sapiens

<220>  
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 <223> n equals a,t,g, or c

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 <212> DNA  
 <213> Homo sapiens

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<210> 26  
 <211> 554  
 <212> DNA  
 <213> Homo sapiens

<400> 26  
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aaaaaaaaaa aaaa 554

<210> 27  
<211> 1319  
<212> DNA  
<213> Homo sapiens

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<210> 28  
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<212> DNA  
<213> Homo sapiens

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<210> 29  
 <211> 1889  
 <212> DNA  
 <213> Homo sapiens

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aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa				1889

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 <212> DNA  
 <213> Homo sapiens

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<210> 31  
 <211> 1162  
 <212> DNA  
 <213> Homo sapiens

<400> 31						
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 <212> DNA  
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<210> 33  
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 <212> DNA  
 <213> Homo sapiens

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 <212> DNA  
 <213> Homo sapiens

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&lt;210&gt; 35

&lt;211&gt; 2053

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 35

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&lt;210&gt; 36

&lt;211&gt; 576

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (538)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (565)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 36

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&lt;210&gt; 37

&lt;211&gt; 1290

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 37

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&lt;210&gt; 38

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 <213> Homo sapiens

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 <211> 1877  
 <212> DNA  
 <213> Homo sapiens

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1877

&lt;210&gt; 40

&lt;211&gt; 2559

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 40

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&lt;211&gt; 2116

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 41

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 <212> DNA  
 <213> Homo sapiens

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 <212> DNA  
 <213> Homo sapiens

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 <212> DNA  
 <213> Homo sapiens

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 <212> DNA  
 <213> Homo sapiens

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 <212> DNA  
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<210> 54  
 <211> 1896  
 <212> DNA  
 <213> Homo sapiens

<400> 54						
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<210> 55  
 <211> 1876  
 <212> DNA  
 <213> Homo sapiens

<400> 55						
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gaaaaaaaaa aaaaaa

1876

<210> 56  
 <211> 1072  
 <212> DNA  
 <213> Homo sapiens

<400> 56  
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 aataaagatg tgaagcaggc cttgaagaat gtcttgagat gaaatattgt catgaccatg 1020  
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<210> 57  
 <211> 652  
 <212> DNA  
 <213> Homo sapiens

<400> 57  
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 caatctctgt agagtgcagg gtggcaagca cccaagggtg gctgaccaag actgcagagt 480  
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<210> 58  
 <211> 1352  
 <212> DNA  
 <213> Homo sapiens

<400> 58  
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aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aa			1352

&lt;210&gt; 59

&lt;211&gt; 1335

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 59

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&lt;210&gt; 60

&lt;211&gt; 2140

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 60

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<210> 61  
 <211> 257  
 <212> DNA  
 <213> Homo sapiens

<400> 61						
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<210> 62  
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 <212> DNA  
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<400> 62						
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ttcattaaaa	aaaaaaaaaa	aaaa				684

<210> 63  
 <211> 1977  
 <212> DNA  
 <213> Homo sapiens

<400> 63						
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 <212> DNA  
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&lt;211&gt; 3067

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 68

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 <212> DNA  
 <213> Homo sapiens

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&lt;213&gt; Homo sapiens

&lt;400&gt; 80

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&lt;210&gt; 81

&lt;211&gt; 1707

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 81

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&lt;210&gt; 82

&lt;211&gt; 1480

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 82

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&lt;210&gt; 83

&lt;211&gt; 425

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 83

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 84

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&lt;210&gt; 85

&lt;211&gt; 2131

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 85

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<400> 88

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 89

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<211> 1617  
 <212> DNA  
 <213> Homo sapiens

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<210> 91  
 <211> 758  
 <212> DNA  
 <213> Homo sapiens

<400> 91  
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<210> 92  
 <211> 2152  
 <212> DNA  
 <213> Homo sapiens

<400> 92  
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<210> 93  
 <211> 758  
 <212> DNA  
 <213> Homo sapiens

<400> 93						
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caaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaa			758

<210> 94  
 <211> 1116  
 <212> DNA  
 <213> Homo sapiens

<400> 94						
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<210> 95  
 <211> 724  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (2)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (3)  
 <223> n equals a,t,g, or c

<400> 95						
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aaaa						724

<210> 96  
 <211> 636  
 <212> DNA  
 <213> Homo sapiens

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<210> 97  
 <211> 1204  
 <212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1187)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1196)

<223> n equals a,t,g, or c

<400> 97

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<210> 98

<211> 1117

<212> DNA

<213> Homo sapiens

<400> 98

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<210> 99

<211> 1092

<212> DNA

<213> Homo sapiens

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<400> 99
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<210> 100

<211> 1450

<212> DNA

<213> Homo sapiens

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<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

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<222> (1439)

<223> n equals a,t,g, or c

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 <223> n equals a,t,g, or c

<220>  
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 <223> n equals a,t,g, or c

<220>  
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 <222> (877)  
 <223> n equals a,t,g, or c

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<210> 104  
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 <212> DNA  
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<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1550)

<223> n equals a,t,g, or c

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<211> 2079

<212> DNA

<213> Homo sapiens

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<222> (1603)

<223> n equals a,t,g, or c

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<221> SITE

<222> (1918)

<223> n equals a,t,g, or c

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<222> (1920)

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<222> (1976)

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<222> (1980)

<223> n equals a,t,g, or c

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 <223> n equals a,t,g, or c

<220>  
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 <223> n equals a,t,g, or c

<400> 105

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 <223> n equals a,t,g, or c

<220>  
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 <223> n equals a,t,g, or c

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aggttttcca tttcagcccc atggtgcag gtggtggccg atgaatgtgt cagtctgctc 2640
agagaaagga caaaaaggaa attattttct aaactgtgtt cactgttttg gtgtgtgtat 2700
ggctctgcat gtgtgtgttt ttgtctctgt ataggtagag gtattcacat cttactccga 2760
ctgtaagggt gtcttacttc atctctgccc ccaccacagt tgccattttg taatgtcctt 2820
ccaacatgga gaagacacga gctctctcca gttggcatca tttgtctttt ttgttgattg 2880
cctcattctc cagtgaactc catctggcca attgattcag aatcaggcaa gatccctgcc 2940
ctttggcaca tccactgaaa ggccaaacag caagtccgag tgagttttta atattaatta 3000
atcacccttt attttttaca cttgagagtg attgtaataa aggctgtcat taataaactt 3060
ggttctacct taaaaaaaaa aaaaaaaaaa actcgacggg ggggccctgt acctcaattc 3120
gcccctatag tgagntgnct caaaa 3144

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<210> 107
<211> 843
<212> DNA
<213> Homo sapiens

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<220>
<221> SITE
<222> (1)
<223> n equals a,t,g, or c

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<220>

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<221> SITE  
 <222> (2)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (3)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (9)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (671)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (695)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (841)  
 <223> n equals a,t,g, or c

<400> 107  
 nnnaacgcnt gtttacaacc cctgctgctt ggttaccac ctcccacctg gggcccctga 60  
 cagatcaggg gacaagcaga tagagggctc accagtgcag tccagtgtat gctgccgggc 120  
 gggccggagc agagtgcagc agatttggct ttttataatc atccaggtgc caggggtgggc 180  
 acgcgtcctg ggatcatcctt ccagcagagg ctcacatcat agcctgtcac cagcagtaat 240  
 tcagcaggag gggttagttt cctccctatg ggatcagcga gggcagctgt ctaagcccca 300  
 ggcacactgc ctagggcgga cgtgggggtg ggggccgtcc tcctagggtt gccctgctct 360  
 tggcaggtga tcagccttca cctccttggt tgggttaggg gggctgcctc ctgtctatgt 420  
 cagagggcctt ctcaaaaaca ggcaccgctg taggggcagc aagatgactt cacttggaaa 480  
 atggaatgta cttaaagcag atcaagccac ctctgtggaga agccattccc ttccaatttg 540  
 gtttaatcct gctgattatt gcaaagagaa agacttagcc tgggtgctaata gactctttaa 600  
 tgcctctgag gacttctaag gtttcctttt ttttctaatac aagaaaagggt aagcctcaag 660  
 ctggtcattc ntctaagttg gaatttaata accngggtt ggtttcataa gaatttaacc 720  
 tttggaagtt gggttaattca ttgggaaggg ccttctgggt ttttcaattt tgggggaagt 780  
 ggattaggaa agtttttcca tttaaaatta aatttaattg gataaaaatt tttttaccgc 840  
 ngg 843

<210> 108  
 <211> 613  
 <212> DNA  
 <213> Homo sapiens

<400> 108  
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 atattttctc tattccatta aattttaatta atttcatttg attttattct gttcttcagg 120  
 aatcttagtt tttatatagt ccaactcatg tactctgctt ccgtcattaa gaattcatag 180  
 tgggagaaat aggtctgttg cttttctcta gaatgcattg ggcaaggctg tttgtttgtt 240  
 tgtttgtttg ctttagacag tcttgctatg ttgccaggc tggagtgcag tggcacaatc 300  
 acagctcact gcaacctctg tctcccggtt tcaagagatt cttctgcctc aacctcccga 360  
 gtagctggga ttacaggcac atggcaacat gcccctgggt aatttttgta tttttagtag 420  
 agatggagtt tcgcatgtt ggccaggctg gtcttgact cctgacctca agtgatctgc 480  
 ctgccttggc cttccaaagt gctgggatta caggactgag ccaccacgcc tggccagggc 540  
 gttttcttaa aaaagtgatt gaaatctgct catgccctgt gccacgtggg tctcacgcag 600  
 gtctgttctc tgc 613

<210> 109  
 <211> 945

<212> DNA  
<213> Homo sapiens

<400> 109  
 gggcagcaga cctgcttcat ttgcgcagtc tgccatgtga atctggaggg gcagccgttc 60  
 tactccaaga aggacagacc cctgtgcaag aagcacgcac acaccatcaa cttgtaggcg 120  
 gccaaggccg cctgtgctga cgaggcccgg agctgtctct gctgctggca acaaaggatt 180  
 cgggaggctg atgtttcttc tgaggggaat ggggagagag aggaagcgac tgagcccttt 240  
 ggaagtataa ttttaggttt tttcttctgt acacagatcg tgcatttgca tagttcagac 300  
 taggagccaa atgaagactc aaaaccaagc tagttattaa tccaagactg gaattgtact 360  
 tcagacattt agagcagaat tccaagaact caaaagtga aagcaacaag cagctttccc 420  
 aaagcgatac acttgctttg gtcaccagag gaggacagag cttagagcag ctgtggagaa 480  
 tctgaagcat tctgaggagt tcttaagcgc tcccctggca aacaaattga agtgccaaac 540  
 agcactcgct gcagggtatt tttagagtca tagctgagag cttgttagct aagaccatt 600  
 gggcttttct caccaaaaaa ggaagtgtta ttccattact agcgtcatgg agctacctct 660  
 gcgcatcaga cttcagacct tgaacaaact taaaaccttc ttgggagccc ggacgtccaa 720  
 agagatgtct tctgggagcc actgggcaat tgccagggt ccaggaaggg ctctggctca 780  
 ggttgcagac agctgagaaa agatggccct gtcagccacc ctctctcagt ctgaaacatc 840  
 caacatcccc agaaggctta gctccttttt gaattgtgat gggaaagtag agttgggttt 900  
 ttctctgctg cgaattcgat atcaagctta tcgataccgt cgacc 945

<210> 110  
<211> 450  
<212> DNA  
<213> Homo sapiens

<400> 110  
 gaggcctgag agccgggcaa gggctgtcgc acatgcgcct tgagggaaga tggcacctgc 60  
 cggctgtctgc tgctgtctgt gcttctgtgg cggcgtctgt gccgcgcgkg gcgcgcgccg 120  
 gcgtgtcctg ctgctgtctg tctgtggggw cctgtccgcc cggctgcggc caggcgccct 180  
 ggccaccgag cactactcgc cgctcgccct gctcaagcag gagctgcakc accggcagca 240  
 gcaggaggcc ccgscgggag gggcgggctg cagcccgcag tccggggact ggggggacca 300  
 gtactctgcc gagtgcgggc agtcattcct tttgmacttc catgactcag actgcgaacc 360  
 ccaaggatca tcaccctgtg actccttgct ttccctcaac actgcgaaga ttctgagcca 420  
 ggccaagtct attgcagaac agaagagatt 450

<210> 111  
<211> 773  
<212> DNA  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (731)  
<223> n equals a,t,g, or c

<400> 111  
 tggaagctaa aacacagggg gctggtgggt tgggtggggg cagataatga tatgcataca 60  
 aattagaggg tctatgcaaa tgagcattgc tgcagtgtgg ctggaggga tcttagttc 120  
 ctaggattct aggatatggg tttcgacccc agaggtgaat gtattgttat tattgttttg 180  
 ttgttggtgt gaatgacaag tcaaaatttg tgggttattg ttgttatcgc caatagtatt 240  
 cttgtcattg ttgcacagta cagagatgaa ggaacagat tttgcaatca gatgatcctg 300  
 ggttctgagt ccactctgcc actcaccagc tatatgacct ccagcaattt ccatcacctc 360  
 tcaatgcttc agtttcccca tcggcaagat ggttgtgggg ggagaggaac aacagtacag 420  
 attcaccatc ccaaattcaa aatgctccaa aatctasgcc ggscgtgggt gctcatacct 480  
 gtaatcccag cactttgrga ggtcaaagwg gacggataac ctgaggtcag gagctccaga 540  
 ccakcctgrc caacatggcg aaaccccatc tctactaaaa atacaaaaaa ttacctgggt 600  
 gtggtggggg gcacctgtaa ccccagctac tcgggagggt gaggcaggaa ccctggaggt 660  
 tgaggttgca gtgagctgag atcacaccac tgcactccag cctgggtgac agagcaaggc 720  
 tcccatctca naaaacaaaa aaacatgctc caaatctga aactctttga gcc 773

<210> 112  
<211> 830  
<212> DNA  
<213> Homo sapiens

<220>  
 <221> SITE  
 <222> (15)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (51)  
 <223> n equals a,t,g, or c

<400> 112  
 caaaaaacat gttcnaaaat ctgaaacttt ttggagccca agtgtgatgc nacaagtggg 60  
 aaattccaca actcatcacr tgtgatagat tgcagtggaa atgcaggcac acaccacgaa 120  
 gtttactcag catcctcaaa ggaaatcccc gtcagtagct atatatcatt ttctcacatg 180  
 ccagataggt atctctcatc ttttactgtt aggtacttct gtgttgaata ggtggaggaa 240  
 aatgattgct ggtagtagt atataaattc agagtcagga aggatgggtga tgcgggctgg 300  
 gtgcagtggc tcatgcctgt aattccaatg tgatacccta ccttgtgttt aacgtgattg 360  
 acyctccctt agctgagarr gccagrcaga ctcyattttg gctycttcry ttgcagtcyc 420  
 tcacccaccc cccttctca aggacttaag ctgactccca gcacatccaa gaatgcgatt 480  
 actgataaga tactgtgaca agctatatcc acarttccca ggaattcgtc yggttgatag 540  
 cacccaaagc ccccgctct atcaccttgt gatasattta aagcccctgc acctggaact 600  
 gtttgtttty ctkttaccat ttatcttttt maytttcttg cctgttttgc ttcyrtaaaa 660  
 ttgcttcagc tckgctccct cytccccctc taaaccaagg tataaaaaga aacctagccc 720  
 cttcttyggg gtgagagaat tttgagcgt agcctctct cagtcgccgg ctaataaagg 780  
 actcctkaat tagtctaaaa aaaaaaaaaa aaaaaaaaaa aaaaactcga 830

<210> 113  
 <211> 646  
 <212> DNA  
 <213> Homo sapiens

<400> 113  
 cttgtgagca ggtgaagctc atctaactag gcatttctat gatgtggctg cttttaacaa 60  
 caacttgttt gatctgtgga actttaaatg ctgggtggatt ccttgatttg gaaaatgaag 120  
 tgaatcctga ggtgtggatg aatactagtg aaatcatcat ctacaatggc taccacagtg 180  
 aagagtatga agtcaccact gaagatgggt atatactcct tgtcaacaga attccttatg 240  
 ggcgaaacaa tgctaggagc acagggtccc ggccagttgt gtatatgcag catgccctgt 300  
 ttgcagacaa tgcctactgg cttgagaatt atgctaattg aagccttgga ttcttcttag 360  
 cagatgcagg ttatgatgta tggatgggaa acagtcgggg aaacacttgg tcaagaagac 420  
 acaaaacact ctacagagaca gatgagaaat tctgggcctt tagttttgat gaaatggcca 480  
 aatatgatct ccaggagta atagacttca ttgtaaataa aactgggtcag gagaaattgk 540  
 atttcattgg acattcactt ggcactacaa tagggtttgt agccttttca ccatgcctga 600  
 actggcacaa agaatcaaaa tgaattttgc cttgggtcct acgate 646

<210> 114  
 <211> 739  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (19)  
 <223> n equals a,t,g, or c

<400> 114  
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 cgtccgcaaa atacctgagc ccaggtaatt tataaagcaa tgaggtttat ttggcttatg 120  
 tttctgcagg ctgtacaagc ttctggtaag ggcctcagga agcttcaca cacggtggaa 180  
 gatgaagggg agccagaatg tgcagattac atggtgagag agtgggaagca agagagaggg 240  
 gcaggagggg ccaggatctt ttcaacaatc agctcatgga tgagcacagt ggctcatgcc 300  
 tgtaatccca gcactttggg agcacaagat gggaggatca cttcagccca agaatttaat 360  
 taagaccaac cagcctgggc aaaaaagtga gactccatct ctacaaaaaa tcaaaaaatt 420  
 aaccagtcac ggtggtgtgt gcctgtggtc caaactacat gggagactga ggtgggagga 480  
 ttgcttgagc ccaggaggtc aagactgcag tgagttatgc tcatgccact gcactccagc 540  
 ctcggcaaca gaatgagaca ctgtcttaaa aaaaagamaa gtgaatttat aaacaaaatt 600  
 ttaaaaaatc agctcttgta aaaactaaga gtgagaactg actcattatt gcaaagataa 660

cactaaccta ttcataaggg atctgtccca ttatccaaac acctcccacc aggccccacc 720  
 tttacaatg ggaatcaaa 739

<210> 115  
 <211> 529  
 <212> DNA  
 <213> Homo sapiens

<400> 115  
 aatttcaaaa acaacgaaac cttcttttgc cccctccgca gcagtcgcct ccgggcttta 60  
 ttgcaagttt acggttccat acaagtaaat ccgaaaaaaa gtgtgtgtgg ggggggtccac 120  
 accactaatt attatggcga ggaagataaa gaagacatgg acagaaggcg gatggctctg 180  
 cggcctggct cccgcagacc gaccgccttc ttcttccatt cgagatggct cgtaccgaac 240  
 ctcttgcct tcttctggg tctctcgggg gctggaccaa tacatctgcc gatgccctgg 300  
 ccgaatggca ggcgacatcg ggtcctggac cccacacgc agctcagtac ccacgaggcc 360  
 ccaggccgct ggaagcctgt agtccgcgg aggatgaaag cctgcccgcg ggttctcctg 420  
 gagtggtag cctctgtcgg aagggggcgc ccacgtcttt ttaatgggcc taacacacca 480  
 gtggaataaa tctctaagat tccaaaaaaa aaaaaaaaaa aaaaaaaaaa 529

<210> 116  
 <211> 751  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (657)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (658)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (691)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (717)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (726)  
 <223> n equals a,t,g, or c

<400> 116  
 tggatcccc gggctgcagg aattcggcac gagtttcagg gcaattttat ttcctctgag 60  
 agcttgtggt cacctctatg ccagtgatta ccaaactaaa tctctagtct tggcttttct 120  
 cttaaactca taaatctatt ccacatttct atcctcgtga tagacttttt tgggatggag 180  
 tttctccaac tcaaacctat tttaccacct ttcccttcaa gcttgctcct cttactaatt 240  
 tctcagtgtc tgctgttggt gccactattt tctcagagat aaactttgga gttctactag 300  
 gtgcctcatt tctctcacct gtcacatcct gtcagtggcc aatgatgtcc attcactgtg 360  
 tacagcctct cctcccatta tttttgccat cgtcttattt caagcaattc ttattacttc 420  
 cctggacttt tggagtagcc ctctaattgg tttacagtct ccaattgttt ttcctaatac 480  
 atcttataaa atactgatga cttttcctaa aaccaatcat gcgaaacctc agcctaaaat 540  
 tcttcattgga gtttgattat ctactgaaga aaatgcaaac ttagcgtgac attccagatt 600  
 ttcttggtcc ccgcctacct ttctaatttt atctaattct tacctttaat tcttggntta 660  
 tacctttctg ataacagtca ctggtttcag ntagaaagct gaaaaggaca ctaacanttt 720  
 ggtagnaatt gctaaatgcc ttatatatgg c 751

<210> 117  
 <211> 660

<212> DNA  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (17)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (67)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (71)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (159)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (209)  
<223> n equals a,t,g, or c

<400> 117						
ctggagcctg	aaagacnctt	accatttttgt	taggaaatgc	taaatgccta	atatatgtca	60
cttaatngca	ngcataggta	agataggttt	aattcccatt	ttaaagggtga	agtaactgag	120
gtttcagaga	gttcagggtta	atttgtccaa	gatcatacna	cttgcaagta	gagcaatcaa	180
ggttgggtga	ttataaatatc	cacatgctnt	ctgtcacggt	gtgttaattc	tttgtgtaca	240
tgtcattttc	ccattgctta	actttgggtta	atcttaaaag	aaggattgct	gaatcaaagt	300
atatatccat	ttaaaatgtg	acacacattt	tcaaactgcc	ttctagaaaag	gttataccag	360
gctaggtgca	gttgtctcat	gcctgtaatc	ctagcacttt	gggaggctga	ggwrrrcgga	420
cagcttgagc	tcaggagtgc	aagaccagcc	tgggcaacat	ggtgaaaccc	tgtctctgta	480
aaaaatacaa	aattggccgg	tcgtgggtgg	gcatgcctat	agtcccagag	attgaggtgg	540
gaggatcgct	tgagcctggg	agatgaaggt	tgacgtgaag	ctgagattgc	accactgcac	600
cacagcctgg	tgacagagtg	aggccctgtc	tcaaaaaaaaa	aaaaaaaaaaa	aaaaactcga	660

<210> 118  
<211> 1488  
<212> DNA  
<213> Homo sapiens

<400> 118						
gagctgcccc	gtccagggtc	atgttcctct	tattttctct	cacgtgtgag	ctggctgcag	60
aagttgctgc	agaagttgag	aaatcctcag	atgggtcctgg	tgctgccag	gaaccacgt	120
ggctcacaga	tgtcccagct	gccatggaat	tcattgtctgc	cactgaggtg	gctgtcatag	180
gcttcttcca	ggatttagaa	ataccagcag	tgcccatact	ccatagcatg	gtgcaaaaat	240
tcccaggcgt	gtcatttggg	atcagcactg	attctgaggt	tctgacacac	tacaacatca	300
ctgggaacac	catctgcctc	tttcgcctgg	tagacaatga	acaactgaat	ttagaggacg	360
aagacattga	aagcattgat	gccaccaaat	tgagccgttt	cattgagatc	aacagcctcc	420
acatgggtgac	agagtacaac	cctgtggcct	ccccagagta	tgaagagAAC	atgcacagat	480
accagaaggc	agccaagctc	ttccagggga	agattctctt	tattctgggtg	gacagtggta	540
tgaaagaaaa	tgggaagggtg	atatcatttt	tcaaactaaa	ggagtctcaa	ctgccagctt	600
tggcaattta	ccagactcta	gatgacgagt	gggatacact	gcccacagca	gaagtttccg	660
tagagcatgt	gcaaaacttt	tgtgatggat	tcctaagtgg	aaaattgttg	aaagaaaatc	720
gtgaatcaga	aggaaagact	ccaaagggtg	aactctgact	tctccttgga	actacatatg	780
gccaagtatc	tactttatgc	aaagtaaaaa	ggcacaaactc	aaatctcaga	gacactaaac	840
aacaggatca	ctaggcctgc	caaccacaca	cacacgcacg	tgacacacag	cacgcacgcg	900
tgacacacac	cacgcgcaca	cacacacaca	cacacacaga	gcttcatttc	ctgtcttaaa	960
atctcgtttt	ctcttcttcc	ttctttttaa	tttcatatcc	tcactcccta	tccaatttcc	1020
ttcttatcgt	gcattcatac	tctgtaagcc	catctgtaac	acacctagat	caaggcttta	1080
agagactcac	tgtgatgcct	ctatgaaaga	gaggcattcc	tagagaaaga	ttgttccaat	1140

ttgtcattta	atatcaagtt	tgtatactgc	acatgactta	cacacaacat	agttcctgct	1200
cttttaaggt	tacctaaggg	ttgaaactct	accttctttc	ataagcacat	gtccgtctct	1260
gactcaggat	caaaaaccaa	aggatggttt	taaacacctt	tgtgaaattg	tctttttgcc	1320
agaagttaaa	ggctgtctcc	aagtccttga	actcagcaga	aatagaccat	gtgaaaactc	1380
catgcttggt	tagcatctcc	aactccctat	gtaaatcaac	aacctgcata	ataaataaaa	1440
ggcaatcatg	ttaggaaaaa	aaaaaaaaaa	agggggggccg	ttttaaaag		1488

<210> 119  
 <211> 656  
 <212> DNA  
 <213> Homo sapiens

<400> 119						
gatggggctg	acgtcaacta	ccagagcaaa	gaagggaaaa	gtcctctgca	catggctgca	60
atccatggcc	gtttcacacg	ctcccagatc	ctcatccaga	atggcagcga	gattgattgt	120
gccgacaaat	ttgggaacac	gccactgcat	gtggctgctc	gatatggaca	cgagctgctc	180
atcagcacc	tcatgaccaa	tggcgcagat	accgcccggc	gtggcatcca	tgacatgttc	240
cccctgcact	tagctgttct	ctttggattc	tctgactgtt	gtcgtaaagct	tctttcctca	300
ggtcagttgt	acagcattgt	gtcttcactc	agcaatgagc	atgtgctttc	agctgggttt	360
gacatcaata	cacctgacaa	ccttggccgt	acctgtcttc	atgctgctgc	ttccggaggg	420
aatgttgaat	gtcttaattt	gctgttgagc	agtggagctg	acttgaggag	gagggacaaa	480
tttggcagga	ccccactgca	ctatgcagct	gctaaccgta	gctaccagtg	tgacagtaaca	540
ttggtgactg	ctggggcagg	tgtcaacgag	gccgactgta	aaggctgctc	tcccctccac	600
tacgctgccc	cttctgacac	ttacaggaga	gcggaacccc	atacaccttc	cagcca	656

<210> 120  
 <211> 1394  
 <212> DNA  
 <213> Homo sapiens

<400> 120						
gttacttaaa	ggtaacatca	cataactaat	gtcttctata	atcctatatt	tattaatgca	60
ttacaactct	gtagattggt	agttactagg	ccagtagcta	ggaattggta	taaatttaaat	120
gcacctttcta	tcctgaataa	ctagcatgga	aaagtgaata	tatgtgtgag	cagatatggc	180
tataaagacc	tatagctttt	gcacttttat	catatataat	caatcctttc	tagttcagtg	240
aattgacccc	atccacaggc	tgattcatct	tttgtttaag	gggcaaatga	aacggtatat	300
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<210> 121  
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 <212> DNA  
 <213> Homo sapiens

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&lt;210&gt; 122

&lt;211&gt; 2793

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 122

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 <211> 511  
 <212> DNA  
 <213> Homo sapiens

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<210> 124  
 <211> 581  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (496)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (580)  
 <223> n equals a,t,g, or c

<400> 124						
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<210> 125  
 <211> 1166  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1163)  
 <223> n equals a,t,g, or c

<400> 125						
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&lt;210&gt; 126

&lt;211&gt; 692

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (32)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 126

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&lt;210&gt; 127

&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 127

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<210> 128  
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 <212> DNA  
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<220>  
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 <222> (199)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (2797)  
 <223> n equals a,t,g, or c

<400> 128						
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aagacttgga	aaattatttt	aaataaacia	ttacatgtaa	ttaaaaaaaa	aaaaaaaaaaa	3660
aatactgcg						3669

&lt;210&gt; 129

&lt;211&gt; 667

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (571)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 129

gatacctctta	ccttggcctc	ccagaatgct	gggattacag	gtaatgagcc	actgcacccg	60
gcttgtagca	ttttttaaaa	agttccttca	tacaggccca	ccactcccag	cctcctttat	120
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cagccacttc	tccaaggagc	cctgattctt	tttattagag	aatgggtatta	gaaaccaagt	240
tctaggcatt	gggtgtgctt	gctactggga	tggtgtggct	tgtaggacct	ttcagctgac	300
tgagcaaggg	atgtacatgt	atgtatacta	aactaagttt	ttctgtatgc	agtcattctgt	360
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tggcttcaga	atacgtattc	ccatggagaa	naaccttatc	aagtagagaa	cagtgcctaa	600
gtgtagttcc	tggtgccttt	agtcttatag	acttcatttc	caaagtttct	tagcaccccc	660
cttcccc						667

&lt;210&gt; 130

&lt;211&gt; 561

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 130

ggggcttgta	aatgtgtgtg	agtttctgag	tgtagggtgcc	gaataaatgt	ttattgatga	60
tgacctaccta	tgcaatctgc	atgggtgctt	tatttctatt	gcttgtgcat	ttgcacatca	120
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cggaccgaga	gtacatttgg	atttctacca	agatatattc	tcctaattca	ccagaacccc	300
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tccacctttc	tcccctctga	cttctgctct	cctcctaaat	gggtctcttt	ccccctgcct	480
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accaagtgca	gacatcaaaa	c				561

&lt;210&gt; 131

&lt;211&gt; 702

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

<221> SITE  
 <222> (693)  
 <223> n equals a,t,g, or c

<400> 131  
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 gactctgtct caaaaaaaaaa gaaaaaaaaa agaaaaagag aaatctatga catcacttgc 120  
 caggctccca tgttcttacc tctgcctgcc ttgccagctc tcctcctgct gtgccttctc 180  
 tcagcccatc tctgcacttc ttcccagtc ttcaacacct gtgcttctct ctgccccag 240  
 gccttccagc caggggggtcc caggcaccag aagtgaattc ccctcaacc ccttctgtct 300  
 gccctccttc ccacgtgaat ccttccttga ttcccttcat ctggtcagct cccattagta 360  
 tgcctctctt gcagcctgcc ctttctcttt tcagtgcgtg atcacaactg tattaggcaa 420  
 tcacctgtct aatgtctgcc ttcttaatta gaacttcaaa ttcacgtggg cataacatcg 480  
 gtctgcctta ttcttctgtg tatcctggat gtcgaacata acacytggca cctgggtggg 540  
 aatgattaaa tatttctgtg aagaatggg aaaataaaa agtaaaaaaa aatgagtgca 600  
 agatacagtg aagtgatgtg gcaatattgc taacttttaa aaawttgtca aagagatact 660  
 gagttcgagg aagaggaaga tagaaattat gcntggaatg ct 702

<210> 132  
 <211> 483  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (416)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (422)  
 <223> n equals a,t,g, or c

<400> 132  
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 agattatgca ggaatttcta ttggaatact gggctgctat gtctcaggag tattttacgc 120  
 attttattgt aataactact ggcgtcaggt gtacttgatc acagtgcttg ctatgatcct 180  
 ggcagtgttc tttgctcaga ttcatcccaa ttacctcacg cagcaatggc aaaggctccg 240  
 ttctatcatc ttttgttctg ttccgggata tggagtgatt cctactcttc actgggtttg 300  
 gctcaatgga ggaattgggtg ctccctattgt acaggacttt gcaccccggt taattgtgat 360  
 tnatatgatt gctcttcttg ctttcttatt ctacatttcc aaagtcccag agcggnaactt 420  
 tncagaatca cttccacggt gaatcatasa agggattgta ccactcgtca cgtgggtggg 480  
 aaa 483

<210> 133  
 <211> 748  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (6)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (15)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (37)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE

<222> (62)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (65)  
 <223> n equals a,t,g, or c

<400> 133  
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 gattcaagcc caccaaatat ggcatatcct tgcagtagtg atgttatatt ggtggcatca 180  
 gtcaacagtg tatgtcatgc agtacagaca tagcaagcct tgtcctgact atgtttcaca 240  
 tttgtgaatt agaatcagga acgaagattc aggggaatgtc tgtcacatct tatggcatcc 300  
 cacctggaca gaatatccga tttgaagatt gtgattgact tccgtaaaac tgtacaactc 360  
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 aatttgaata gaagttttaca tccaaaagtc ataataagac aaataatgaa aaactccaaa 480  
 gtcactgatt ataaagaata tgcaatccat ttgggattta ttgcatttaa agaaaacaga 540  
 ttaaaacagt gcttacgtga agtaccaaaa cctaaaataa accaagcaga gtagctgact 600  
 tgtaagaaaa ctgctctgcc tgggtgaactt cagcatagaa gagtgggctc caccttagat 660  
 tttccaccag caagaggaca acagtctatc actcttaaac aataaacagg gtaagactga 720  
 aaaaaaaaaa aaaaaaaaaa aaactcga 748

<210> 134  
 <211> 652  
 <212> DNA  
 <213> Homo sapiens

<400> 134  
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 gaccgcgccg cggggcctgg ctggctcagg gctacctcct tccgcctagg acccccctt 120  
 cggtgactcc cgattccctg tccataggctg cggtgccccg ggaggcgggt cgccagagta 180  
 gcagacagag ctctttaatg ggtgtcttct agggcggggt ctgtttgtgc atcatttggg 240  
 tccccacaca ctctctatga ggtggcgaaa gccattatgc ctatgggtgc tgcacacaca 300  
 gggggaaact gaggcccagg caggacagcc ccttgccctg ggtgggggct gggttgtcct 360  
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 gccagagtc tgcagccagg ccagaccyt ggccgtgtccg tccgggggatg ctggacagta 480  
 ctctccctc cagccctcat aagtcatkgt cattcggats tgcatttccc cagccctct 540  
 ccttctaast ggggggcact gtggccact gtgcccctt ctcttcccat tcttccccc 600  
 tacaccatt ccagacatcc cagagttaac aaaacccaaa aaaaaaaaaa aa 652

<210> 135  
 <211> 3006  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (2700)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (2711)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (2808)  
 <223> n equals a,t,g, or c

<400> 135  
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 gtatgatgtc atgactcatt tgtaacagat ccagcctcag ggacagccct gtaaggcagc 120  
 aagtggggct ggctccaaat gggatatgag ctccagaatct ttggtaaggc agaactgaac 180  
 tgggctgaga ggtgggtctta aggcctgggc aggcctctatt ctctctggac tggctgcagc 240

ctgcagtcta	ggagaggccc	agtacagcct	ggagctcctg	agccttgctca	acaggcagtg	300
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ctgtgc						3006

&lt;210&gt; 136

&lt;211&gt; 720

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (657)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 136

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ggttgctggg	catgtcggca	ggcgtgtgtg	gcattcacagc	cttgggtggg	cagctggact	240
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cgggcctsgt	ggggctgggg	ctgagctgcc	tcgctgggca	gctgctgtac	tactctngcc	660
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<210> 137  
 <211> 463  
 <212> DNA  
 <213> Homo sapiens

<400> 137						
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tctctgcttt	catggactgt	ttgtgggtgg	ggtgaggtgg	tcagtgggtcc	tccttgtgct	180
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gcaccatcag	gtgctgttca	aacccctctg	agccccgagc	tgcttgkgat	ctcatttcaa	300
ctccatgcag	cccctctagg	gcagttttat	ttccccattt	tacagatggg	aaaagagaaa	360
ctcagattgc	gtaacatgcc	caaggaagca	ccggyccag	wgtttgyttt	gtttgwtttg	420
sttttgagga	gsagmctctg	tcaccagggc	tggagwgctg	gag		463

<210> 138  
 <211> 699  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (155)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (656)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (658)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (664)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (678)  
 <223> n equals a,t,g, or c

<400> 138						
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tggggctaca	ctaccacaaa	ggcacatctc	tccttagggc	tggwgggctt	tgctggsaag	600
gagaacatga	aagaattgya	tgyasagagy	tccagaagct	tctagacatt	tcctgnctng	660
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<210> 139

<211> 950  
 <212> DNA  
 <213> Homo sapiens

<400> 139  
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<210> 140  
 <211> 2952  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (3)  
 <223> n equals a,t,g, or c

<220>  
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 <222> (12)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (199)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (2938)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (2952)  
 <223> n equals a,t,g, or c

<400> 140  
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 cagtgaaccc accccttttc tgccctgcag cgtaamcatt cccagcctc ctacaggcag 180  
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aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaancc	2940
ccgggggggg	gn					2952

&lt;210&gt; 141

&lt;211&gt; 776

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (631)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (755)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (761)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (768)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (775)

<223> n equals a,t,g, or c

<400> 141

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gtgtgtttta	gtccttatga	ggcctgggtg	agtcctttag	cagtctcaac	gaaaaccaat	180
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tcatacaata	tctcaagaaa	gaaagtacct	cagattattg	gggtttgttt	tctgcctgtc	360
ccttctctgt	aagatattag	cccttcaatt	accagctctc	ttagtagcaa	tgaagtctaa	420
gttttgcctt	gctagcccca	tgagactgcc	aaaagcttta	cttgcttctc	ctgcctgttg	480
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cataaatctt	gractcttca	gtcctggctg	ntttggtagc	tttccaatgg	cttyacatgg	660
acacttccca	accccgggcc	cacgatctgg	cytttcttgg	aagtctcaac	taagcctggg	720
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<210> 142

<211> 702

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (3)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (14)

<223> n equals a,t,g, or c

<400> 142

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agaagtgtta	ctagactacc	cactgctacc	tacagtgagc	cccattctgc	acacagaggc	180
tgcggactcc	tttttcccaa	tcatagacca	gaatgcttgt	gaaagaagat	gtggctgttc	240
tgcaggttgg	agctctagga	tcggaagaac	tcactctgtat	cacatatgat	ccagctgaaa	300
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gatacagagt	ttcactctgt	cacccaggct	ggagttagagt	gggtgccatct	cagctcattg	600
caacctctgc	cccctgggtt	caagcaattc	tcctgcctca	gccttycgag	tagctgggat	660
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<210> 143

<211> 798

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> n equals a,t,g, or c

<400> 143

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ggcagtttca	aggttactat	tctcatgatt	caacacatcc	tcaaggagtg	agattcagtc	120
tgtgtaagtg	tatcatgact	ttctataaca	cgccttgtea	tgcactcttc	taccctgcta	180
gaattggagt	ctggcctcag	ctgggttcta	ccagcagtac	tgccatcacc	tcactctcat	240
ctgccccatc	tggtgtttts	gaaccacttg	tgctctctga	aatgcatatg	ttgaagtctt	300
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gggccgagga	gagaggctct	agagaaacca	acccaatgac	atttcgtctt	ggatttccag	540

ccccagaat	tactggaaaa	tacatttttc	ttgttttaggc	cacccaatct	gtactacttt	600
gttatggcaa	ccctagcaaa	ctaattgcagt	caccaaccca	gggtgaaaat	gggacattcc	660
caactctagc	tcttaggcca	agcttatttg	taatagattc	ttgttttcaa	aggatataga	720
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aaaaaaaaag	gcggccgc					798

<210> 144  
 <211> 566  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (442)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (484)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (535)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (537)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (549)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (564)  
 <223> n equals a,t,g, or c

<400> 144						60
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ttagtagaga	cggggttttg	ccatgtttggc	caggctgggc	tcgaactcct	gacctcacat	240
gatctgcgca	cctaggcctc	ccaaagtgtt	gggattacag	gtgtgagcca	tcgcacccgg	300
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ataacatcsa	ttgtaaatat	cnaataaaaa	ttagattcct	ttaatTTTTT	taaagacaca	540
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gaactcccna	gcttaagcca	tctnca				

<210> 145  
 <211> 1939  
 <212> DNA  
 <213> Homo sapiens

<400> 145						60
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tttccaaaac	cgggcagagg	ggtggcagct	cttgtgcctg	gggtccctgc	cagtccgtgg	240
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gtgggccttg	ccccagccc					1939

&lt;210&gt; 146

&lt;211&gt; 619

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (124)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (128)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 146

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ctactccaag	cacagtcatt	cctccaaagt	gctgggttcc	tcctggccca	gccggggcca	120
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caggacaatg	ctgggttatga	tttctgccgt	ccccctgggac	tggcctcatt	ccttaagagg	420
caagattaaa	aaaaaataaa	aagccaggca	cgagggtctca	tgccctataat	cccagcactc	480
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tgcgcctgtg	gttccagct					619

&lt;210&gt; 147

&lt;211&gt; 2032

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 147

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<210> 148  
 <211> 1048  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (965)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1024)  
 <223> n equals a,t,g, or c

<220>  
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 <222> (1026)  
 <223> n equals a,t,g, or c

<400> 148	tggtgaatg	ggtttgatag	ttgtgcttct	atttcccaac	ctctgtatgt	gtacctttca	60
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	acaaagacta	gagtcttaca	tccaaatgct	caatggagtc	agtgtgacaa	cggctgtacc	480
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&lt;210&gt; 149

&lt;211&gt; 701

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (691)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 149

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&lt;210&gt; 150

&lt;211&gt; 617

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 150

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ccttcttagc	ctcctgacat	gagtcgtctg	gaaagagcat	ccaaacaaac	aagkaataaa	600
taaataaata	aactcaa					617

&lt;210&gt; 151

&lt;211&gt; 881

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (864)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (869)

&lt;223&gt; n equals a,t,g, or c

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gaagggaaga ggcgtcctgc caaggcctgg tcaggcagga gaaccaggct ctgctgccac      180
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tgcaagcttg agccagagcc ccgcctttgg gtggtgcctg gggcactccc acagggtgtag      300
cactcccaaa gcaagactcc agacagcgga gaacctcatg cctggcacct gaggtaccca      360
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ccatcaactt tcagagctat catgagccaa cctcacccca cagggcctca gtcgccacca      540
tgtgggcctc tccagtgcaa accaccgagc attccaccat gaccggtcac agctacaaat      600
ccagagacca tcaatcctgc tagagtgcag ggwggcaagc acccaagggg ggctgaccaa      660
gactgcagag tctctcccat cttcaggtcc attcagcctc ctggcattta actaccagca      720
tccagtggtc cccaaggaat cccttcctag cctcctgaca tgagtctgct ggaaagagca      780
tccaaacaaa caagtaataa ataaataaat aaactcaaaa aaaaaaaaaa aaaaaaaaaa      840
aaaaaaaaaa aaaagggcgg ccgntctana ggatccaagc t                        881

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<210> 152

<211> 576

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (436)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (488)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (510)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (531)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (551)

<223> n equals a,t,g, or c

<400> 152

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cggctgggaa caccaccctg gccccgaacg tgactacagc ctcgctctcca ccgccacca      180
ccacgcagct cccggtgtca ccgacgactc tctcgccgct gccggtcacc actccagcac      240
cagatatctg tggaagccga aacagttgtg tttcctgtgt tgatggtaat gctacctgct      300
tttggataga atgtaaaggt aaaagctact gttcagataa ttcaacagct ggtgattgca      360
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caacttccac cacagntact acatcaggta caactaatac cactctatct ccaactatac      480
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<210> 153

<211> 637

<212> DNA

<213> Homo sapiens

<400> 153

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gcttttactg	tccctccctt	ccagtgtaat	ctagatccct	gtctctatta	cccagcactg	480
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gtcagtgagc	acttgaaatg	tgaactgaat	tttaagattc	gatttaatat	taattttatt	600
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<210> 154  
 <211> 800  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (4)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (19)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (61)  
 <223> n equals a,t,g, or c

<220>  
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 <222> (100)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (150)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (156)  
 <223> n equals a,t,g, or c

<400> 154						
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cccatggatg	ctcctctgaa	gagactttcn	tcattnactg	ccgaggcccc	atgaawcaat	180
gtctggtasc	caccggwayt	masgaaccgr	aaaaccmaag	ctatatggta	agaggctgtg	240
caaccgcctm	aatgtgcmma	matgccmacc	tgggtgacgc	cytcagcatg	aaccacattg	300
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aaaaaaaaaa	aaaaactcga					800

<210> 155  
 <211> 684  
 <212> DNA  
 <213> Homo sapiens



<220>  
 <221> SITE  
 <222> (668)  
 <223> n equals a,t,g, or c

<400> 155  
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 cagtcctccc accccagcct cccaagtagc tgggactaca gatactcaac accacaccgg 240  
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 ggctcaggcg atctgcccac ctcaacctcc cacagtgtcg gtattacagg cgtgaagcca 360  
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 gatatcanaa atgggtgccc gcgg 684

<210> 156  
 <211> 1574  
 <212> DNA  
 <213> Homo sapiens

<400> 156  
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<210> 157  
 <211> 2050  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (878)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE

&lt;222&gt; (1573)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 157

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aaaaaaaaaa						2050

&lt;210&gt; 158

&lt;211&gt; 638

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 158

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ctactgagtg	ctatggctat	gacctggaca	ttaaactggc	cctcataggt	tcagacctgg	600
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&lt;210&gt; 159

&lt;211&gt; 1332

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (11)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (50)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1323)

<223> n equals a,t,g, or c

<400> 159

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tgcaaagaaa	atatgggtgc	agaattcttg	caattttaatt	ttagtaaatt	ctttatcttt	180
tttattacca	taccttaaaa	ttgctatgca	catattttct	gtctcagtta	tgtactcaac	240
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gactattttg	cgtcacttat	tttatgaata	tcactattgg	atatgctctt	ttgcaccaat	360
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tctgctgttg	tcataaagca	ttttggttct	cttctgatac	tttttgaaga	ctcatccatt	540
tttcattctt	tcagcaaaca	tgaccatgat	accccatata	gaccagatat	tgtggtacag	600
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aagtgtactc	gtgccgaatt	cctgcagccc	gggggatcca	ctagttctag	agcggccgcc	1260
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tengcgtatc	at					1332

<210> 160

<211> 1267

<212> DNA

<213> Homo sapiens

<400> 160

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gcaccagccc	ccagtcacgg	agagcacgag	catgggcacc	aagccaggcc	tcccaggctg	720
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ttgagaatgg	actctacgct	caggcagggg	agaggcctcc	tcacactggg	cccggcctca	960
ctcttttccc	tgaccctcgg	ggggccaggg	ccatggaagg	acccttagga	gttcgatgag	1020
agagaccatg	aggccactgg	gctttccccc	tcccaggcct	cctgggtgtc	atccccctac	1080
tttaattctt	gggcctccaa	taagtgtccc	ataggtgtct	ggccaggccc	acctgtctcg	1140
gatgtgggtc	gtgtgcgtgt	gtgggcacag	gtgtgagtg	gtgagtgaca	gttaccat	1200
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aaaaaaa						1267

<210> 161  
 <211> 476  
 <212> DNA  
 <213> Homo sapiens

<400> 161  
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 gagaagggca gcaaggctgg ctggccgcag ccctctgttg ctggacacga cttggcaagg 180  
 ccgaggggatc tgagggctgg gctactctcg agggctgccca gggtcccagc ttgctgcagg 240  
 gaaatgaagg ggggtgccgc ctgaacaggc acatgcctaa gcaagggtatt gacgcttgga 300  
 taaagctggc aaccaccagg agaagccttt ttgggatttt tcaaatacctt cgycatccga 360  
 gctgtgatga tggagtggar cgtkgcacgg gccatttga gttctgtkkg ctccatcggm 420  
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<210> 162  
 <211> 1040  
 <212> DNA  
 <213> Homo sapiens

<400> 162  
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 acttcccac cactgttcaa aagctgtgat ttttgtctcc ctttcccacc ctccagccaa 180  
 ggagcagccc tgcccagggg gcattaggtg tgggtaccgc gggagcacc cgttcctgga 240  
 cccagtggt gcatttctg gctgaggaag ggtggtcatc ccagctcctg ccctaccctc 300  
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 ggcggggcct cagcacagct tgggtgctggt aagaggaagc ccgtggttct ggctaggctc 420  
 tcatgtccag acagcgggga ccaggggaaa acccagcccc ttctgtaatc ccccttcatt 480  
 tectacettc cttctctctc tgttttagcaa aggagggcag ctcacttgga tgtccttaca 540  
 acgccccctg ccccaggttg agcaataaga aaccagaacc ttgcggccca gtggcccggg 600  
 ccagttcag cgcctcccc ctctctgcc tggggccatt gagcccagcc tccagggccc 660  
 ggggtgcgtt gcaggccagt ggccactgtc cgggctgtga tggcaccaag gcaggtggag 720  
 caccaggtac cacacagctg ggcttcccac caggctttcc cgcgggggtc tcagggagct 780  
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 catacagtat taggtgagga tggatgcggg cgctgtcctt gccgggaagt cactgttgaa 900  
 gttgcagtgg cttgttcaca cctgtgggaa gagaagtga gactttctcc ttgcattaaa 960  
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 tctagatcgc gagcggccgc

<210> 163  
 <211> 621  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (4)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (8)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (24)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (60)  
 <223> n equals a,t,g, or c

<220>

<221> SITE  
 <222> (119)  
 <223> n equals a,t,g, or c

<400> 163  
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 cagcctttcc cagccttgct tagggccggg ttgggagaat cccaccccgc agggctgtgg 180  
 tgagggttga acggaggggtg tgtgggtgagg gttgagcgga ggggtgtgtga tgcgtggtga 240  
 ggggttagca ataagaaacc agaacccttg agcctccagg gccraatgc gtttgcaggc 300  
 cagtggccac tgtccgggct gtgatggcac caaggcagg ggagcaccag gtaccacaca 360  
 gctgggcttc ccaccaggct ttcccgcggg ggtctcagg agcttctccc cagcgtgct 420  
 sggagtctgc aggaactggc cttgttctcc ttagcccgct actccataca gtattaggtg 480  
 aggatggatg cgggcgctgt ccttgccggg aagtcactgt tgaagttgca gtggcttgtt 540  
 cacacctgtg ggaagagaag tgaagacttt ctcttgcatt taaaaagtct gaactgagaa 600  
 aaaaaaaaaa aaaaaactcg a 621

<210> 164  
 <211> 601  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (592)  
 <223> n equals a,t,g, or c

<400> 164  
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 taagtakaca gcaactgagc cctccctccc accccaggy tcccagagca acagggagca 120  
 ggagcatag gacctggccg sagccaggaa tctacactga cgggtcagc ccatgaagta 180  
 tcttgggctg aagtcacagg atgagactgt ttgtatctgt aactgtcctt gtcattctgtc 240  
 ttgcagattt agaagaggaa tcagaaagct gggacaactc tgagtctgaa gaggaggaga 300  
 aagccccctgt gttgccagag agtacagaag ggcgggagct gaccagggc ccggcagagt 360  
 cctcctctct ctcaggctgt gggagctggc agccccggaa gctgccagtc ttcaagtccc 420  
 tccggcacat gaggcgagta ggcggcagg gcacagcgca tcaggagctc aggaggagag 480  
 ccaatcatgg gctgtccctg cccacacgct ttgctctggt accctccacc ttcaaaaccc 540  
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 t 601

<210> 165  
 <211> 3337  
 <212> DNA  
 <213> Homo sapiens

<400> 165  
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 atactgtgga tacttagaga aattcaaagc atatatatca ttggaatttt ccgaaatccc 180  
 ttttatccga aggatgtgca aactgtgact gtattctttg agaagcaaac taggctcatg 240  
 aagattggta ttgtcagacg gatcttctga acttttagtat cactttttgc catgatagca 300  
 tttctttcat tggacagttc cttacaaggg ctccactcag tgtctgtctg tattggattc 360  
 acaagagcct ttagaatggt wtggcagaat wcagaaaawg cyttattgga gacmgtcatt 420  
 gtatcaacag tactattgat ctccagtaca gacatatggt ggaacagaag cctggatata 480  
 ggactcagac tcttactggg ttggtatccat acgtgatcgt ttgattcagt tcatctctaa 540  
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 aacaactgcc actttatgta tactcaacat tgtcttttct ccattcgtgt tggatcatcat 660  
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 ggtgggggtt ccccgacctt ttcagagttg gccaggagca gcakgcacca cagcctgtgt 780  
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 tgcaatggca gctggaaagt taggtctcct cctacctgga tctcattact tgggccgttt 900  
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ggagttcagt	tgttcacatt	ctcacttagt	atgcttacc	gcagagtggg	ggactagctg	1680
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aattgccaag	gacaaagt	taaaagactt	ttatgttcat	acagtaata	cttgtttatt	1860
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tggtgttttg	ccttgggtctg	ttgctttgga	ctggctcaca	gaaaagccag	aactgtttca	1980
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cattgggttg	gtatctgatg	aaaagtggaa	ggaagcaatt	ttacaagaaa	agccatactt	2160
gttttctctg	gggtatgatt	ctaataatggg	aatttacact	gggagagtgc	ttagccttca	2220
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agtcagaagg	agatggaaga	aaatttttat	aatacgatct	gaattttatt	ttcattctct	3300
tcttgcttag	gaacgtttta	cagatacatg	taagggg			3337

&lt;210&gt; 166

&lt;211&gt; 510

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (503)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (504)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (508)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 166

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acagatttct	aaaagcaatt	cccaggctat	tgtgggctat	ggtttgatga	tattacttat	120
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cttttatccg	aaggatgtgc	aaactgtgac	tgtattcttt	gagaagcaaa	ctaggctcay	240
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atttctttca	ttggacagtt	ccttacaagg	gctccactca	gtgtctgtct	gtattggatt	360
cacaagagcc	tttagaatgg	tatggcagaa	tacagaaaat	gctttattgg	agacagtcac	420
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agggggaacc cacttcgtga acnncgtntc

510

<210> 167  
 <211> 1367  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1339)  
 <223> n equals a,t,g, or c

<400> 167  
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 gcctcggttg ctaactttga gtacatcatc gcagaaaaaa gaggggaagaa taacaccgtg 180  
 ggggtgatcc aactgaaccg ccccaaggcc ctcaatgcac tttgcgatgg cctgattgac 240  
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 accggcgggg ataaggcctt tgcagctgga gctgatatca aggaaatgca gaacctgagt 360  
 ttccaggact gttactccag caagtctctt aagcactggg accacctcac ccaggtaag 420  
 aagccagtca tcgctgctgt caatggctat gcctttggcg ggggctgtga gcttgccatg 480  
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 ggaaccatcc caggtgcggg cggcaccag agactaccc gtgctgttgg gaagtcgctg 600  
 gcgatggaga tggctctcac cggtgaccgg atctcagccc aggacgcaa gcaagcagg 660  
 cttgtcagca agatttgtcc tgttgagaca ctggtggaag aagccatcca gtgtgcagaa 720  
 aaaattgccg gcaattctaa aattgtagta gcgatggcca aagaatcagt gaatgcagct 780  
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 gccactgatg accggaagaa agggatgacc gcgtttgtgg aaaagagaaa ggccaacttc 900  
 aaagaccagt gagaaccagc tgcccctgct tcacacctct gcttggagag gacaagtga 960  
 gcctgtcagt tttagaagca agtaaatcat cctcttttca agagcagtgt ccgtggtgtg 1020  
 cagttcctct ccaattgctg cgtggtcgtg gcccgacctc tcacggcatg acagccttcg 1080  
 tcaccagccc tgtgagggtc ctgactggag cactctctaa atctaagatt ctgctgagga 1140  
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 tgtgtccctg ccgctgaaga atggggctgc tctgagggaa acgctgtctc ttcatacaga 1260  
 tgctgattaa agtgatagcg attcagatta aaaaaaaaaa aaaaaaaag ggattcgaaa 1320  
 tccaatttat ggatacctng accccaaggg gggcccgtaa cccattc 1367

<210> 168  
 <211> 594  
 <212> DNA  
 <213> Homo sapiens

<400> 168  
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 ccgaccgggc cactggaagt tggagcctcc gccgagtcgc agacaacgcc tccgggaggg 120  
 ccttcctgat gcgcttgctt gctccctggt ctctctgcat ggggaaggag tgttcccagc 180  
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 aaggakgtga ggtggctgcg gtccccattc ccgcagcgct cccaggctgt tcacatattc 480  
 cgggatggga aggaccagga tgaagatctg atgccggaat ataaggggag gacggtgcta 540  
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<210> 169  
 <211> 684  
 <212> DNA  
 <213> Homo sapiens

<400> 169  
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 gttctctccg agttgacttt tctgtgcctt tgtgcatgct cttatctcct ctgcttgaa 120  
 tgtccttttc agcctgtcaa actccttcaa aatccagctc agatgttaca ttttctttaa 180  
 gcaactcctga cccaccccc caaatagact tagtccagcc ttcttctggg ttcccacagc 240  
 actcagtaca gtttgaaagg tcctttataa yagtcattat tacatttttc aaaaataatt 300  
 tcatattcat taacctcatt agattataag cacctcaatt atgtagactg ttttatcact 360

gctgwcccg	cacagcacct	ggcacagtta	gctgttcaag	acatctctgt	tgagtgggta	420
aatgaatgag	ttccactcca	ggttcctgtg	tttgkgacct	ccaggggcct	cttctcttcc	480
cttccccttc	tcacgtaggc	tgatgccctg	gtcttccagc	tatgcactct	acctgcctct	540
cgawgctcta	agccgatgtg	tccatcattt	ggctgtttgc	atattctgat	tcatgacatt	600
ctcctgcaca	gtgctggctg	acactctgta	gcccatacata	tctgacttct	ctggccagcc	660
tgtatgccta	ccatcagctc	gccc				684

<210> 170  
 <211> 1494  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (345)  
 <223> n equals a,t,g, or c

<400> 170						
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tcaactgtgg	ctgagatggg	atztatgttg	caaaacaaag	tcctgtttat	cctttcctct	180
cctcttctca	aggagaagga	tggaaatctct	tttgagagctg	ggagccttcc	tgcttttgat	240
tgggggagtg	gtgacacaag	cgctccctta	gccgcattgg	ctgggtgtctc	actagggtcat	300
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gctcacatga	tttttggttc	ttatgaagg	gctttttgtg	taggtgggtg	tcagatttgg	780
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aatactgtta	atctccagaa	atataagtga	accttagctt	ttctgttggg	ggctttttaa	1320
ctttttatga	tgggaaaatg	tgtgaatttt	ctcctgggaa	agtatagact	ggagacttag	1380
ataccagtag	atgaattgag	gaatttctgt	gtagcagttt	aatatagaaa	agagttagct	1440
gtccatgagg	aagggtctta	agaacaacaa	taactaccaa	aaaaaaaaaa	aaaa	1494

<210> 171  
 <211> 610  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (602)  
 <223> n equals a,t,g, or c

<400> 171						
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cagcccagag	ccggggctat	ggggcccagc	gggcacctgg	tggcctgagt	tatcctgcag	180
cctctcccac	gccccatgca	gccttctctg	ctgacctggg	gtccaacatg	gccattggct	240
atgggagcag	cctggccg	cagggcaagg	agctgggtga	taagaacatc	gaccgcttca	300
tccccatcac	caagctcaag	tattactttg	ctgtggacac	catgtatgtg	ggcagaaagc	360
tgggcctgct	gttcttcccc	tacctacacc	aggactggga	agtgcagtac	caacaggaca	420
ccccggtggc	ccccgcgttt	gacgtcaatg	ccccggacct	ctacattcca	gcaatggctt	480
tcatcaccta	cgttttgggtg	gctggcttgc	gctggggacc	caggataggt	tytccccagm	540
cctcctgggg	ctgcaagcga	gctcagccct	ggctgctgac	cctgaagtgc	tggcatctgc	600
tnagcttatt						610



<210> 172  
 <211> 654  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (594)  
 <223> n equals a,t,g, or c

<400> 172  
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 catgtcagtg ttgactttac aagaatatga attcgaaaag cagttcaacg agaatgaagc 180  
 catccaatgg atgcaggaaa actggaagaa atctttcctg ttttctgctc tgtatgctgc 240  
 ctttatattc ggtggtcggc acctaatagaa taaacgagca aagtttgaac tgaggaagcc 300  
 attagtgtc tcgtctctga cccttgcaat cttcagtata ttcggtgctc ttcgaactgg 360  
 tgcttatatg gtgtacattt tgatgaccaa aggcctgaag cagtcagttt gtgaccagkg 420  
 tttttacaat ggacctgtca gcaaattctg ggcttatgca tttgtgctaa gcaaagcacc 480  
 cgaactagga gatacaatat tcattattct gaggaagcag aagctgatct tcctgcactg 540  
 gtatcaccac atcactgtgc tcctgtactc ttggtactcc tacaagagaca tggnttgccg 600  
 gggagggttg ttcatgacta tgaactatgg cgtgcacgcc gtgatgtact ctta 654

<210> 173  
 <211> 2046  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (33)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (96)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (100)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (113)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (122)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (131)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1986)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE

&lt;222&gt; (1993)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2019)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 173

cctgggtattc	aggactgaat	tgggaagtctg	agnatcagtg	tggagccata	tctcggctgg	60
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ancactaaca	nggaacaaat	tcaaggacaa	cctgtytttg	agccaggcag	cctcagacac	180
ctgcctgtgg	ccccckctcc	acttctcctg	cccggtatgcc	agtgtctccga	gctcagacag	240
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agccca						2046

&lt;210&gt; 174

&lt;211&gt; 1439

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (37)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (61)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (73)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 174

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&lt;210&gt; 175

&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 175

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tcagactatc	aacc					675

&lt;210&gt; 176

&lt;211&gt; 8446

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2333)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3087)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (4356)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6401)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 176

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&lt;210&gt; 177

&lt;211&gt; 730

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 177

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&lt;210&gt; 178

&lt;211&gt; 621

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 178

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&lt;210&gt; 179

&lt;211&gt; 558

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (133)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (395)

&lt;223&gt; n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (408)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (409)  
 <223> n equals a,t,g, or c

<400> 179  
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 aagactctgt ctcaaaaa 558

<210> 180  
 <211> 1513  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1481)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1513)  
 <223> n equals a,t,g, or c

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<210> 181  
 <211> 777  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (35)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (155)  
 <223> n equals a,t,g, or c

<400> 181  
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 aatagcagct gacaactttc tgtgcctttt cctttctgtt gaaaaggcat agaaagtctt 660  
 gggaacataa acattttttac ccttttctat gccatttatt ttgtaaaaat cctattttaac 720  
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<210> 182  
 <211> 1909  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1902)  
 <223> n equals a,t,g, or c

<400> 182  
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caaaaaagta	ggtgagaact	ggcttcctca	ttgtcccagg	atgtcaaata	ctaatagacat	1560
aagagctcac	ttacgtgccca	aaattcactt	ttatactagt	ttttcagtg	tttaatatatt	1620
gtaacttaaa	ttttaaaact	cgtattttaca	aacactactg	taacttcagt	gaaactgaat	1680
tgtgcgattg	aagctttttg	cttatcatag	tattttattac	actacttaat	tcagtaaata	1740
tataaaagta	gccttcaatt	tatttttata	ttattttaca	tgtttttacc	tgcagttgtg	1800
tatgtgaatt	taccttggtg	atcgagatgt	catgctaagg	accaataaac	tatcactgaa	1860
caaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa		1909

<210> 183  
 <211> 773  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (47)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (62)  
 <223> n equals a,t,g, or c

<400> 183						
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atcggaaccc	tctatcacta	ctattaaatc	cacaatttaa	atcaccatca	tctcttatct	180
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ctttctgaat	tagtcagggt	tctccataga	aagataatca	attggttttt	tatatattta	600
aggagatttt	attatggaga	attagcatat	gcaaatatgg	agaccacaat	gtgccatcta	660
caagctggag	acccaagaca	gctgggtggg	taattcartc	tgagtcgcaa	ggctgagagc	720
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<210> 184  
 <211> 614  
 <212> DNA  
 <213> Homo sapiens

<400> 184						
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ggagaagaca	atgaagggtt	ctacaattaa	gattttgctc	tattttttcc	atcatatcta	180
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gtacattgca	gacattagta	catgacacct	ctaatacagt	ttatgttcct	ttccttttta	300
ctttatacga	aataaaaatc	acagttaaca	attatcaagt	gcttactgtc	aggcactgtg	360
ccaagcactt	tccttgcat	acataatttg	aatctcatgg	taaccctata	agtacagtta	420
ccaccttcat	tttacaatat	agaagaactg	aaacagagaa	caatgggtgc	aattaacatt	480
ttaaaagtct	ttctatgggc	cattcacagt	gcaagtactt	ttcatgcatt	awctcagtta	540
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aaaaagatct	tgga					614

<210> 185  
 <211> 437  
 <212> DNA  
 <213> Homo sapiens

<400> 185						
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caactacaaa	gggcttaaca	aacttcgtaa	attggagata	tataggacat	tgtacctaac	180
ctaatagaaa	cttaaacatt	ttttagttat	gkatgkcagt	ttttaaccat	gttccataga	240

ggaatgttaa	caatgtctaa	aaaatcagkg	tcatacaaaa	tacgttattt	cagccaggca	300
tggcagctca	tgccggtaat	cctagtgtt	tgggaggctg	aggcaggagg	atcacttgaa	360
gccaggcaag	accatatagk	gagactygt	ctctgcaaaa	aaaaaaaaag	ggcggcscce	420
cttttttttt	tttttta					437

&lt;210&gt; 186

&lt;211&gt; 587

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (534)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 186

gacatccatt	gaagctgcaa	caccaccccc	cgccacttca	cctccttcct	gacatgctct	60
gctcctcctt	tctccccctc	agcactgctg	ccatctgggc	tgcattattc	tcgggtatgg	120
gggtgttccg	acattcccca	tcagaaggaa	aaagatccct	gaaaagtagc	aggtgcttac	180
atttctggcc	tctaccacc	ggctgcagta	gtccccacc	accctgcaat	gtgacaacca	240
aaaatgtctc	tagatgttgc	cagaagtcct	ctagagatgg	gagggtagca	ctgccacccc	300
gctgagaatt	cctgctgtca	ctggagtggg	ggctgttttc	tctcccatgc	ctctggtacc	360
ttgggggtcc	ccccgtctcc	caagggtctg	ttccaccacc	ctgtccatcc	atcccattg	420
gtccccagga	ggtttttagct	ccgggcttcc	tgtctccac	accactcctc	acagttctcc	480
atgatttcaa	catccaggtg	ggcgacgcag	cctctcggtt	ccttgaccct	ctngtgcac	540
ctgctgcttc	taccgggcca	accagtactc	ctaggagccc	tcacaat		587

&lt;210&gt; 187

&lt;211&gt; 1706

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1424)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1665)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1688)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 187

ggcttcctcg	ggtactcggc	cactcggggc	atcgcgggcg	cctttctagc	cgctgtccca	60
aggggttggtc	tcgcgctttc	ggctgcgagc	tctctgtggt	gctggcagcg	acatgtggcg	120
cctccccgga	ctcctgggccc	gagctcttcc	ccgtacactg	ggacctagcc	tctggagggt	180
gactcctaag	tccaccagcc	cagatgggccc	tcagactacc	tcctccactt	tgctggttcc	240
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ccatggatgg	aaggatgcct	tccaatggat	gtcttcccg	gtctccccga	acaccctatg	360
ggatgccata	tcttggggca	ctctggccgt	gctggccctg	cagctggcaa	ggcagatcca	420
cttcaggca	tccctgccag	caggacctca	gcgggtagaa	cactgctcct	ggcacagtcc	480
cctggaccgt	ttcttctcat	ctcccttgtg	gcacccatgc	tcctcactgc	gacaacacat	540
cctccccagc	cccgatggcc	cagctcccag	gcacactggc	ctcaggggaa	ccaggcttgg	600
ccaggaagaa	gcctcagctc	agccccggaa	cttctcacac	aactctttga	gaggagctcg	660
tcctcaggac	ccctctgagg	aaggctcccg	tgattttggc	ttcctgcatg	ccagtagtag	720
catcgagtcc	gaggcaaaac	cagcccagcc	tcagcccact	ggtgaaaagg	aacaagataa	780
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agccttttct	tacttccaga	aagctgcagc	ccgcgggtac	agcaaagcgc	agtacaatgc	960
gggcttgtgt	catgagcatg	gcagaggcac	ccccagggac	attagcaagg	cggtccttta	1020
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agcaggaacc	tcacgcctac	cacatgcctc	gagcacaggc	aaccttgggc	tcctctgcag	1560
aagtgggcat	ytccgagcca	gcctggaagc	ctccagcagg	gctattcccc	cacamccyta	1620
cccaytggaa	aggagtgttk	taagaytagg	ttttggytaa	ggaanttcca	gcggggggtt	1680
caagtttncc	caaggcaatt	ttcaag				1706

&lt;210&gt; 188

&lt;211&gt; 1150

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (407)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (413)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 188

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atctgaggac	atctctgtgc	caggccagaa	accgcccacc	tgagttcct	tctccgggat	120
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aaaaaaaaag						1150

&lt;210&gt; 189

&lt;211&gt; 1233

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 189

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tctctgtgcc	aggccagaaa	ccgcccacct	gcagttcctt	ctccgggatg	gacgtggggc	120
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atgccttctg	gtactgccat	tctttttttt	ttttttttca	agtattggaa	gggggtggga	1140
gatataataa	taaatcatga	aatcaataca	waaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1200
aaaaaaaaaa	aaaaaaaaaa	aaaaagggcg	gcc			1233

&lt;210&gt; 190

&lt;211&gt; 633

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (7)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (11)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (596)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (597)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (598)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (599)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (600)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (601)

&lt;223&gt; n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

<220>  
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<222> (603)  
<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

<220>  
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<222> (606)  
<223> n equals a,t,g, or c

<220>  
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<222> (607)  
<223> n equals a,t,g, or c

<220>  
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<222> (608)  
<223> n equals a,t,g, or c

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<222> (609)  
<223> n equals a,t,g, or c

<220>  
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<222> (610)  
<223> n equals a,t,g, or c

<220>  
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<222> (611)  
<223> n equals a,t,g, or c

<220>  
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<222> (612)  
<223> n equals a,t,g, or c

<220>  
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<222> (613)  
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<220>  
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<222> (614)  
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<220>

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 <222> (615)  
 <223> n equals a,t,g, or c

<220>  
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 <222> (616)  
 <223> n equals a,t,g, or c

<220>  
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 <222> (617)  
 <223> n equals a,t,g, or c

<220>  
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<220>  
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 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (620)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (621)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (622)  
 <223> n equals a,t,g, or c

<220>  
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 <222> (623)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (624)  
 <223> n equals a,t,g, or c

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 tctgtatgtg ttctgtgtcc cttgcatgtg tgcgtgttag agtgagcgcg tatgcatcaa 360  
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 nnnnnnnnnn nnnnnnnnnn nnnnaaaaaa aaa 633

<210> 191  
 <211> 705  
 <212> DNA  
 <213> Homo sapiens

<400> 191  
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 tggaatgcca tagatgaggg gcccaagagg gacattgtca aggaacttga ggtagccatt 420  
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 ctcttctctg aggatgaatc cagttcattc cataagcggc aatttccagt ttctaagaca 540  
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 <211> 2901  
 <212> DNA  
 <213> Homo sapiens

<400> 192  
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 ctgcacgtcg accctgacct gtacacactc ttgtttggag agagtgtgtt gaatgatgca 180  
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 tgtgagttcc cgatgctgga aaccggcctg tttttcctgc tttcttggag tgccttccctg 420  
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 gcacattata cctacaacaa tctgtcttcg gattccaaaa taagaactaa acagttgttt 540  
 gaatttatga actttttggc ggagaacgtc atcttctgtt acatgggcct ggcactgttc 600  
 acgttccaga atcatatctt taatgctctt tttatacttg gagcctttct agcaattttt 660  
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 <213> Homo sapiens

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<220>  
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&lt;211&gt; 490

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 195

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 196

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&lt;210&gt; 197

&lt;211&gt; 3746

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 197

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&lt;211&gt; 91

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 198

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Cys Gly Tyr Ser Gly Asp Met Lys Gly Val Cys Trp Gly Arg Ser Asp
          20              25              30

```

```

His Ser Leu Leu Pro Ser Glu Ile Leu Leu Pro Pro Ala Pro Cys Pro
      35              40              45

```

```

Ser Ser Ala Val Leu His Asn Pro Pro Pro Thr Pro His Leu Pro Ser
      50              55              60

```

```

Pro Val Leu Val Arg Ile Gln Glu Ala Pro Thr Trp Ala Gln Arg Ser
      65              70              75              80

```

```

Ser Leu Gly Ala Ser Pro Leu His Lys Gly Asp
          85              90

```

&lt;210&gt; 199

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 199

```

Met Ser Cys Thr Leu Leu Ile Cys Thr Val Val Leu Gly Val Thr Thr
  1              5              10              15

```

```

Pro Ala Ile Gly Pro Ala Ala Pro Ser Leu Leu Ala Thr Pro Pro Gln
      20              25              30

```

```

Ala Ala Ala Ala Thr Met Gln Pro Arg Leu Gly Arg Ala Ala Gly Ala
      35              40              45

```

Ala

&lt;210&gt; 200

&lt;211&gt; 95

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 200

```

Met Val Pro Cys Arg Lys Thr Leu Leu Phe Leu Trp Val Gly Ser Leu

```

108

1	5	10	15
Cys Arg Asp Val Gly Ser Trp Ser Gly Trp Pro Phe Gly Leu Ser Thr	20	25	30
Ala Thr Gln Pro Arg Leu Arg Leu Gly Lys Gln Thr Gly Ala Gly Gln	35	40	45
Ala Arg Arg Ala Cys Arg Thr Val Ile Leu Arg Cys Gly Ser Cys Cys	50	55	60
Arg Gly Arg Arg Thr Gly Ser Val Val Ala Trp Ser Ser Leu Pro Gln	65	70	75
Arg Thr Ser Ala Ala Glu Leu Arg Trp Arg Pro Trp Gly Pro Val	85	90	95

<210> 201  
 <211> 175  
 <212> PRT  
 <213> Homo sapiens

<400> 201  
 Met Ala Thr Pro Ser Gly Leu Gly Ala Leu Leu Leu Leu Leu Leu Leu  
 1 5 10 15  
 Pro Thr Ser Gly Gln Glu Lys Pro Thr Glu Gly Pro Arg Asn Thr Cys  
 20 25 30  
 Leu Gly Ser Asn Asn Met Tyr Asp Ile Phe Asn Leu Asn Asp Lys Ala  
 35 40 45  
 Leu Cys Phe Thr Lys Cys Arg Gln Ser Gly Ser Asp Ser Cys Asn Val  
 50 55 60  
 Glu Asn Leu Gln Arg Tyr Trp Leu Asn Tyr Glu Ala His Leu Met Lys  
 65 70 75 80  
 Glu Gly Leu Thr Gln Lys Val Asn Thr Pro Phe Leu Lys Ala Leu Val  
 85 90 95  
 Gln Asn Leu Ser Thr Asn Thr Ala Glu Asp Phe Tyr Phe Ser Leu Glu  
 100 105 110  
 Pro Ser Gln Val Pro Arg Gln Val Met Lys Asp Glu Asp Lys Pro Pro  
 115 120 125  
 Asp Arg Val Arg Leu Pro Lys Ser Leu Phe Arg Ser Leu Pro Gly Asn  
 130 135 140  
 Arg Ser Val Val Arg Leu Ala Val Thr Ile Leu Asp Ile Gly Pro Gly  
 145 150 155 160  
 Thr Leu Phe Lys Val Arg Thr Gln Gly Ser Ser Lys Val Lys Cys  
 165 170 175

<210> 202  
 <211> 126  
 <212> PRT  
 <213> Homo sapiens

<400> 202

109

Met Ala Ala Phe Ala Thr Ala His Leu Leu Tyr Val Trp Ala Phe Gly  
 1 5 10 15  
 Phe Ser Pro Leu Gln Pro Gly Leu Leu Leu Ile Ile Leu Ala Pro  
 20 25 30  
 Gly Pro Tyr Leu Ser Leu Val Leu Gln His Leu Glu Pro Asp Met Val  
 35 40 45  
 Leu Pro Val Ala Ala Tyr Gly Leu Ile Leu Met Ala Met Leu Trp Arg  
 50 55 60  
 Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu Phe Thr  
 65 70 75 80  
 Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro Leu Pro  
 85 90 95  
 His Ala His Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln Leu Leu  
 100 105 110  
 Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp  
 115 120 125

<210> 203  
 <211> 187  
 <212> PRT  
 <213> Homo sapiens

<400> 203  
 Met Trp Cys Ala Ser Pro Val Ala Val Val Ala Phe Cys Ala Gly Leu  
 1 5 10 15  
 Leu Val Ser His Pro Val Leu Thr Gln Gly Gln Glu Ala Gly Gly Arg  
 20 25 30  
 Pro Gly Ala Asp Cys Glu Val Cys Lys Glu Phe Leu Asn Arg Phe Tyr  
 35 40 45  
 Lys Ser Leu Ile Asp Arg Gly Val Asn Phe Ser Leu Asp Thr Ile Glu  
 50 55 60  
 Lys Glu Leu Ile Ser Phe Cys Leu Asp Thr Lys Gly Lys Glu Asn Arg  
 65 70 75 80  
 Leu Cys Tyr Tyr Leu Gly Ala Thr Lys Asp Ala Ala Thr Lys Ile Leu  
 85 90 95  
 Ser Glu Val Thr Arg Pro Met Ser Val His Met Pro Ala Met Lys Ile  
 100 105 110  
 Cys Glu Lys Leu Lys Lys Leu Asp Ser Gln Ile Cys Glu Leu Lys Tyr  
 115 120 125  
 Glu Lys Thr Leu Asp Leu Ala Ser Val Asp Leu Arg Lys Met Arg Val  
 130 135 140  
 Ala Glu Leu Lys Gln Ile Leu His Ser Trp Gly Glu Glu Cys Arg Ala  
 145 150 155 160  
 Cys Ala Glu Lys Thr Asp Tyr Val Asn Leu Ile Gln Glu Leu Ala Pro  
 165 170 175  
 Lys Tyr Ala Ala Thr His Pro Lys Thr Glu Leu

110

180

185

<210> 204  
 <211> 38  
 <212> PRT  
 <213> Homo sapiens

<400> 204  
 Met Thr Trp Gly Thr Lys Ala Thr Trp Tyr Leu Ala Ser Ser Ser Ser  
           1                  5                  10                  15  
 Cys Gly Ser Tyr Cys Pro Pro Pro Cys Trp Trp Ala Ser Ser Gly Cys  
                   20                  25                  30  
 Thr Gly Pro His Arg Thr  
           35

<210> 205  
 <211> 163  
 <212> PRT  
 <213> Homo sapiens

<400> 205  
 Met Gly Gly Met Ile Ile Val Leu Leu Ile Cys Ile Val Trp Phe Pro  
           1                  5                  10                  15  
 Leu Leu Phe Met Ser Leu Ile Lys Ser Val Ala Gly Val Ile Asn Gln  
                   20                  25                  30  
 Pro Leu Asp Val Ser Val Thr Ile Thr Leu Gly Gly Tyr Gln Pro Ile  
           35                  40                  45  
 Phe Thr Met Ser Ala Gln Gln Ser Gln Leu Lys Ile Met Asp Gln Gln  
           50                  55                  60  
 Ser Phe Asn Lys Phe Ile Gln Ala Phe Ser Arg Asp Thr Gly Ala Met  
           65                  70                  75                  80  
 Gln Phe Leu Glu Asn Tyr Glu Lys Glu Asp Ile Thr Val Ala Glu Leu  
                   85                  90                  95  
 Glu Gly Asn Ser Asn Ser Leu Trp Thr Ile Ser Pro Pro Ser Lys Gln  
           100                  105                  110  
 Lys Met Ile His Glu Leu Leu Asp Pro Asn Ser Ser Phe Ser Val Val  
           115                  120                  125  
 Phe Ser Trp Ser Ile Gln Arg Asn Leu Ser Leu Gly Ala Lys Ser Glu  
           130                  135                  140  
 Ile Ala Thr Asp Lys Leu Ser Phe Pro Leu Lys Asn Ile Asn Ser Lys  
           145                  150                  155                  160  
 Glu Tyr Arg

<210> 206  
 <211> 369  
 <212> PRT  
 <213> Homo sapiens

111

&lt;400&gt; 206

Met Ala Phe Lys Leu Leu Ile Leu Leu Ile Gly Thr Trp Ala Leu Phe  
 1 5 10 15  
 Phe Arg Lys Arg Arg Ala Asp Met Pro Arg Val Phe Val Phe Arg Ala  
 20 25 30  
 Leu Leu Leu Val Leu Ile Phe Leu Phe Val Val Ser Tyr Trp Leu Phe  
 35 40 45  
 Tyr Gly Val Arg Ile Leu Asp Ser Arg Asp Arg Asn Tyr Gln Gly Ile  
 50 55 60  
 Val Gln Tyr Ala Val Ser Leu Val Asp Ala Leu Leu Phe Ile His Tyr  
 65 70 75 80  
 Leu Ala Ile Val Leu Leu Glu Leu Arg Gln Leu Gln Pro Met Phe Thr  
 85 90 95  
 Leu Gln Val Val Arg Ser Thr Asp Gly Glu Ser Arg Phe Tyr Ser Leu  
 100 105 110  
 Gly His Leu Ser Ile Gln Arg Ala Ala Leu Val Val Leu Glu Asn Tyr  
 115 120 125  
 Tyr Lys Asp Phe Thr Ile Tyr Asn Pro Asn Leu Leu Thr Ala Ser Lys  
 130 135 140  
 Phe Arg Ala Ala Lys His Met Ala Gly Leu Lys Val Tyr Asn Val Asp  
 145 150 155 160  
 Gly Pro Ser Asn Asn Ala Thr Gly Gln Ser Arg Ala Met Ile Ala Ala  
 165 170 175  
 Ala Ala Arg Arg Arg Asp Ser Ser His Asn Glu Leu Tyr Tyr Glu Glu  
 180 185 190  
 Ala Glu His Glu Arg Arg Val Lys Lys Arg Lys Ala Arg Leu Val Val  
 195 200 205  
 Ala Val Glu Glu Ala Phe Ile His Ile Gln Arg Leu Gln Ala Glu Glu  
 210 215 220  
 Gln Gln Lys Ala Pro Gly Glu Val Met Asp Pro Arg Glu Ala Ala Gln  
 225 230 235 240  
 Ala Ile Phe Pro Ser Met Ala Arg Ala Leu Gln Lys Tyr Leu Arg Ile  
 245 250 255  
 Thr Arg Gln Gln Asn Tyr His Ser Met Glu Ser Ile Leu Gln His Leu  
 260 265 270  
 Ala Phe Cys Ile Thr Asn Gly Met Thr Pro Lys Ala Phe Leu Glu Arg  
 275 280 285  
 Tyr Leu Ser Ala Gly Pro Thr Leu Gln Tyr Asp Lys Asp Arg Trp Leu  
 290 295 300  
 Ser Thr Gln Trp Arg Leu Val Ser Asp Glu Ala Val Thr Asn Gly Leu  
 305 310 315 320  
 Arg Asp Gly Ile Val Phe Val Leu Lys Cys Leu Asp Phe Ser Leu Val  
 325 330 335  
 Val Asn Val Lys Lys Ile Pro Phe Ile Ile Leu Ser Glu Glu Phe Ile

112

340	345	350
Asp Pro Lys Ser His Lys Phe Val	Leu Arg Leu Gln Ser	Glu Thr Ser
355	360	365

Val

<210> 207  
 <211> 85  
 <212> PRT  
 <213> Homo sapiens

<400> 207  
 Met Asp Thr Tyr Phe Ile Leu Trp Ala Ile Pro Val Thr Ile Ile Ile  
 1 5 10 15  
 Cys Phe Ser Trp Leu Glu Tyr Ser Gln Thr Trp Ala Leu Gly Ala Ser  
 20 25 30  
 Cys Ser Leu Pro Gln Cys Pro Phe Asp Val Met Leu Ser Leu Phe Leu  
 35 40 45  
 Val His Pro Tyr Phe Pro Thr Val Trp Asp His Leu Cys Phe Pro His  
 50 55 60  
 Pro Ser Pro Glu Ser Ser Pro Phe Ser Lys Cys Ser Leu Val Ala Trp  
 65 70 75 80  
 Leu Glu Asn Gly Ala  
 85

<210> 208  
 <211> 172  
 <212> PRT  
 <213> Homo sapiens

<400> 208  
 Met His Gly Ala Arg Leu Phe Val Cys Leu Phe Val Cys Phe Arg Gln  
 1 5 10 15  
 Ser Cys Tyr Val Ala Gln Ala Gly Val Gln Trp His Asn His Ser Ser  
 20 25 30  
 Leu Gln Pro Leu Ser Pro Gly Phe Lys Arg Phe Phe Cys Leu Asn Leu  
 35 40 45  
 Pro Ser Ser Trp Asp Tyr Arg His Met Ala Thr Cys Pro Trp Leu Ile  
 50 55 60  
 Phe Val Phe Leu Val Glu Met Glu Phe Arg His Val Gly Gln Ala Gly  
 65 70 75 80  
 Leu Gly Leu Leu Thr Ser Ser Asp Leu Pro Ala Leu Ala Phe Gln Ser  
 85 90 95  
 Ala Gly Ile Thr Gly Leu Ser His His Ala Trp Pro Gly Arg Phe Leu  
 100 105 110  
 Lys Lys Val Ile Glu Ile Cys Ser Cys Pro Val Pro Arg Gly Ser His  
 115 120 125



113

Ala Gly Leu Phe Ser Ala Pro Gly Leu Pro Cys Glu Ser Gly Gly Ala  
 130 135 140

Ala Val Leu Leu Gln Glu Gly Gln Thr Pro Val Gln Glu Ala Arg Thr  
 145 150 155 160

His His Gln Leu Val Gly Gly Gln Gly Arg Leu Cys  
 165 170

<210> 209  
 <211> 829  
 <212> PRT  
 <213> Homo sapiens

<400> 209  
 Met Ala Pro Ala Gly Cys Cys Cys Cys Cys Cys Phe Trp Gly Gly Ala  
 1 5 10 15  
 Val Ala Ala Ala Gly Ala Ala Arg Arg Val Leu Leu Leu Leu Leu Leu  
 20 25 30  
 Gly Val Leu Ser Ala Arg Leu Arg Pro Gly Ala Leu Ala Thr Glu His  
 35 40 45  
 Tyr Ser Pro Leu Ala Leu Leu Lys Gln Glu Leu Gln His Arg Gln Gln  
 50 55 60  
 Gln Glu Ala Pro Ala Gly Gly Gly Gly Cys Ser Pro Gln Ser Gly Asp  
 65 70 75 80  
 Trp Gly Asp Gln Tyr Ser Ala Glu Cys Gly Glu Ser Ser Phe Leu Asn  
 85 90 95  
 Phe His Asp Ser Asp Cys Glu Pro Lys Gly Ser Ser Pro Cys Asp Ser  
 100 105 110  
 Leu Leu Ser Leu Asn Thr Glu Lys Ile Leu Ser Gln Ala Lys Ser Ile  
 115 120 125  
 Ala Glu Gln Lys Arg Phe Pro Phe Ala Thr Asp Asn Asp Ser Thr Asn  
 130 135 140  
 Glu Glu Leu Ala Ile Ala Tyr Val Leu Ile Gly Ser Gly Leu Tyr Asp  
 145 150 155 160  
 Glu Ala Ile Arg His Phe Ser Thr Met Leu Gln Glu Glu Pro Asp Leu  
 165 170 175  
 Val Ser Ala Ile Tyr Gly Arg Gly Ile Ala Tyr Gly Lys Lys Gly Leu  
 180 185 190  
 His Ile Leu Ser Pro Leu Gly Arg Ile Asn Glu Ala Val Asn Asp Leu  
 195 200 205  
 Thr Lys Ala Ile Gln Leu Gln Pro Ser Ala Arg Leu Tyr Arg His Arg  
 210 215 220  
 Gly Thr Leu Tyr Phe Ile Ser Glu Asp Tyr Ala Thr Ala His Glu Asp  
 225 230 235 240  
 Phe Gln Gln Ser Leu Glu Leu Asn Lys Asn Gln Pro Ile Ala Met Leu  
 245 250 255  
 Tyr Lys Gly Leu Thr Phe Phe His Arg Gly Leu Leu Lys Glu Ala Ile

260					265					270					
Glu	Ser	Phe	Lys	Glu	Ala	Leu	Lys	Gln	Lys	Val	Asp	Phe	Ile	Asp	Ala
		275					280					285			
Tyr	Lys	Ser	Leu	Gly	Gln	Ala	Tyr	Arg	Glu	Leu	Gly	Asn	Phe	Glu	Ala
	290					295					300				
Ala	Thr	Glu	Ser	Phe	Gln	Lys	Ala	Leu	Leu	Leu	Asn	Gln	Asn	His	Val
305						310					315				320
Gln	Thr	Leu	Gln	Leu	Arg	Gly	Met	Met	Leu	Tyr	His	His	Gly	Ser	Leu
			325						330					335	
Gln	Glu	Ala	Leu	Lys	Asn	Phe	Lys	Arg	Cys	Leu	Gln	Leu	Glu	Pro	Tyr
			340					345					350		
Asn	Glu	Val	Cys	Gln	Tyr	Met	Lys	Gly	Leu	Ser	His	Val	Ala	Met	Gly
		355					360					365			
Gln	Phe	Tyr	Glu	Gly	Ile	Lys	Ala	Gln	Thr	Lys	Val	Met	Leu	Asn	Asp
	370					375					380				
Pro	Leu	Pro	Gly	Gln	Lys	Ala	Ser	Pro	Glu	Tyr	Leu	Lys	Val	Lys	Tyr
385						390					395				400
Leu	Arg	Glu	Tyr	Ser	Arg	Tyr	Leu	His	Ala	His	Leu	Asp	Thr	Pro	Leu
				405					410					415	
Thr	Glu	Tyr	Asn	Ile	Asp	Val	Asp	Leu	Pro	Gly	Ser	Phe	Lys	Asp	His
			420					425					430		
Trp	Ala	Lys	Asn	Leu	Pro	Phe	Leu	Ile	Glu	Asp	Tyr	Glu	Glu	Gln	Pro
		435					440					445			
Gly	Leu	Gln	Pro	His	Ile	Lys	Asp	Val	Leu	His	Gln	Asn	Phe	Glu	Ser
	450					455					460				
Tyr	Lys	Pro	Glu	Val	Gln	Glu	Leu	Ile	Cys	Val	Ala	Asp	Arg	Leu	Gly
465						470					475				480
Ser	Leu	Met	Gln	Tyr	Glu	Thr	Pro	Gly	Phe	Leu	Pro	Asn	Lys	Arg	Ile
				485					490					495	
His	Arg	Ala	Met	Gly	Leu	Ala	Ala	Leu	Glu	Val	Met	Gln	Ala	Val	Gln
			500					505					510		
Arg	Thr	Trp	Thr	Asn	Ser	Lys	Val	Arg	Met	Asn	Gly	Lys	Thr	Arg	Leu
		515					520					525			
Met	Gln	Trp	Arg	Asp	Met	Phe	Asp	Ile	Ala	Val	Lys	Trp	Arg	Arg	Ile
	530					535					540				
Ala	Asp	Pro	Asp	Gln	Pro	Val	Leu	Trp	Leu	Asp	Gln	Met	Pro	Ala	Arg
545						550					555				560
Ser	Leu	Ser	Arg	Gly	Phe	Asn	Asn	His	Ile	Asn	Leu	Ile	Arg	Gly	Gln
				565					570					575	
Val	Ile	Asn	Met	Arg	Tyr	Leu	Glu	Tyr	Phe	Glu	Lys	Ile	Leu	His	Phe
			580					585					590		
Ile	Lys	Asp	Arg	Ile	Leu	Val	Tyr	His	Gly	Ala	Asn	Asn	Pro	Lys	Gly
		595					600					605			
Leu	Leu	Glu	Val	Arg	Glu	Ala	Leu	Glu	Lys	Val	His	Lys	Val	Glu	Asp

115

610					615					620					
Leu	Leu	Pro	Ile	Met	Lys	Gln	Phe	Asn	Thr	Lys	Thr	Lys	Asp	Gly	Phe
625					630					635					640
Thr	Val	Asn	Thr	Lys	Val	Pro	Ser	Leu	Lys	Asp	Gln	Gly	Lys	Glu	Tyr
				645					650					655	
Asp	Gly	Phe	Thr	Ile	Thr	Ile	Thr	Gly	Asp	Lys	Val	Gly	Asn	Ile	Leu
			660					665					670		
Phe	Ser	Val	Glu	Thr	Gln	Thr	Thr	Glu	Glu	Arg	Thr	Gln	Leu	Tyr	His
			675					680					685		
Ala	Glu	Ile	Asp	Ala	Leu	Tyr	Lys	Asp	Leu	Thr	Ala	Lys	Gly	Lys	Val
Leu	Ile	Leu	Ser	Ser	Glu	Phe	Gly	Glu	Ala	Asp	Ala	Val	Cys	Asn	Leu
705					710					715					720
Ile	Leu	Ser	Leu	Val	Tyr	Tyr	Phe	Tyr	Asn	Leu	Met	Pro	Leu	Ser	Arg
				725					730					735	
Gly	Ser	Ser	Val	Ile	Ala	Tyr	Ser	Val	Ile	Val	Gly	Ala	Leu	Met	Ala
			740					745					750		
Ser	Gly	Lys	Glu	Val	Ala	Gly	Lys	Ile	Pro	Lys	Gly	Lys	Leu	Val	Asp
			755				760					765			
Phe	Glu	Ala	Met	Thr	Ala	Pro	Gly	Ser	Glu	Ala	Phe	Ser	Lys	Val	Ala
			770				775					780			
Lys	Ser	Trp	Met	Asn	Leu	Lys	Ser	Ile	Ser	Pro	Ser	Tyr	Lys	Thr	Leu
785					790					795					800
Pro	Ser	Val	Ser	Glu	Thr	Phe	Pro	Thr	Leu	Arg	Ser	Met	Ile	Glu	Val
				805					810					815	
Leu	Asn	Thr	Asp	Ser	Ser	Pro	Arg	Cys	Leu	Lys	Lys	Leu			
			820					825							

<210> 210  
 <211> 108  
 <212> PRT  
 <213> Homo sapiens

<400> 210  
 Met Thr Ser Gln Asn Leu Trp Val Ile Val Val Ile Ala Asn Ser Ile  
 1 5 10 15  
 Leu Val Ile Val Ala Gln Tyr Arg Asp Glu Gly Asn Arg Phe Cys Asn  
 20 25 30  
 Gln Met Ile Leu Gly Ser Glu Ser Thr Leu Pro Leu Thr Ser Tyr Met  
 35 40 45  
 Thr Ser Ser Asn Phe His His Leu Ser Met Leu Gln Phe Pro His Arg  
 50 55 60  
 Gln Asp Gly Cys Gly Gly Arg Gly Thr Thr Val Gln Ile His His Pro  
 65 70 75 80  
 Lys Phe Lys Met Leu Gln Asn Leu Gly Arg Ala Trp Trp Leu Ile Pro  
 85 90 95

116

Val Ile Pro Ala Leu Trp Glu Val Lys Val Asp Gly  
 100 105

<210> 211  
 <211> 153  
 <212> PRT  
 <213> Homo sapiens

<400> 211  
 Met Met Trp Leu Leu Leu Thr Thr Thr Cys Leu Ile Cys Gly Thr Leu  
 1 5 10 15  
 Asn Ala Gly Gly Phe Leu Asp Leu Glu Asn Glu Val Asn Pro Glu Val  
 20 25 30  
 Trp Met Asn Thr Ser Glu Ile Ile Ile Tyr Asn Gly Tyr Pro Ser Glu  
 35 40 45  
 Glu Tyr Glu Val Thr Thr Glu Asp Gly Tyr Ile Leu Leu Val Asn Arg  
 50 55 60  
 Ile Pro Tyr Gly Arg Thr His Ala Arg Ser Thr Gly Pro Arg Pro Val  
 65 70 75 80  
 Val Tyr Met Gln His Ala Leu Phe Ala Asp Asn Ala Tyr Trp Leu Glu  
 85 90 95  
 Asn Tyr Ala Asn Gly Ser Leu Gly Phe Leu Leu Ala Asp Ala Gly Tyr  
 100 105 110  
 Asp Val Trp Met Gly Asn Ser Arg Gly Asn Thr Trp Ser Arg Arg His  
 115 120 125  
 Lys Thr Leu Ser Glu Thr Asp Glu Lys Phe Trp Ala Phe Ser Phe Asp  
 130 135 140  
 Glu Met Ala Asn Met Ile Ser Gln Glu  
 145 150

<210> 212  
 <211> 87  
 <212> PRT  
 <213> Homo sapiens

<400> 212  
 Met Arg Phe Ile Trp Leu Met Phe Leu Gln Ala Val Gln Ala Ser Gly  
 1 5 10 15  
 Lys Gly Leu Arg Lys Leu Pro His Thr Val Glu Asp Glu Gly Glu Pro  
 20 25 30  
 Glu Cys Ala Asp Tyr Met Val Arg Glu Trp Lys Gln Glu Arg Gly Ala  
 35 40 45  
 Gly Gly Ala Arg Ile Phe Ser Thr Ile Ser Ser Trp Met Ser Thr Val  
 50 55 60  
 Ala His Ala Cys Asn Pro Ser Thr Leu Gly Ala Gln Asp Gly Arg Ile  
 65 70 75 80  
 Thr Ser Ala Gln Glu Phe Asn

117

85

<210> 213  
 <211> 90  
 <212> PRT  
 <213> Homo sapiens

<400> 213  
 Met Asp Arg Arg Arg Met Ala Leu Arg Pro Gly Ser Arg Arg Pro Thr  
   1                  5          10          15  
 Ala Phe Phe Phe His Ser Arg Trp Leu Val Pro Asn Leu Leu Ala Phe  
           20                  25                  30  
 Phe Leu Gly Leu Ser Gly Ala Gly Pro Ile His Leu Pro Met Pro Trp  
           35                  40                  45  
 Pro Asn Gly Arg Arg His Arg Val Leu Asp Pro His Thr Gln Leu Ser  
       50                  55                  60  
 Thr His Glu Ala Pro Gly Arg Trp Lys Pro Val Ala Pro Arg Arg Met  
   65                  70                  75                  80  
 Lys Ala Cys Pro Gln Val Leu Leu Glu Trp  
                   85                  90

<210> 214  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<400> 214  
 Met Met Ser Ile His Cys Val Gln Pro Leu Leu Pro Leu Phe Leu Pro  
   1                  5          10          15  
 Ser Ser Tyr Phe Lys Gln Phe Leu Leu Leu Pro Trp Thr Phe Gly Val  
           20                  25                  30  
 Ala Leu

<210> 215  
 <211> 245  
 <212> PRT  
 <213> Homo sapiens

<400> 215  
 Met Phe Leu Leu Phe Leu Leu Thr Cys Glu Leu Ala Ala Glu Val Ala  
   1                  5          10          15  
 Ala Glu Val Glu Lys Ser Ser Asp Gly Pro Gly Ala Ala Gln Glu Pro  
           20                  25                  30  
 Thr Trp Leu Thr Asp Val Pro Ala Ala Met Glu Phe Ile Ala Ala Thr  
   35                  40                  45  
 Glu Val Ala Val Ile Gly Phe Phe Gln Asp Leu Glu Ile Pro Ala Val  
   50                  55                  60  
 Pro Ile Leu His Ser Met Val Gln Lys Phe Pro Gly Val Ser Phe Gly

65				70				75				80			
Ile	Ser	Thr	Asp	Ser <sub>85</sub>	Glu	Val	Leu	Thr	His <sub>90</sub>	Tyr	Asn	Ile	Thr	Gly <sub>95</sub>	Asn
Thr	Ile	Cys	Leu <sub>100</sub>	Phe	Arg	Leu	Val	Asp <sub>105</sub>	Asn	Glu	Gln	Leu	Asn <sub>110</sub>	Leu	Glu
Asp	Glu	Asp <sub>115</sub>	Ile	Glu	Ser	Ile	Asp <sub>120</sub>	Ala	Thr	Lys	Leu	Ser <sub>125</sub>	Arg	Phe	Ile
Glu	Ile <sub>130</sub>	Asn	Ser	Leu	His	Met <sub>135</sub>	Val	Thr	Glu	Tyr	Asn <sub>140</sub>	Pro	Val	Ala	Ser
Pro <sub>145</sub>	Glu	Tyr	Glu	Glu	Asn <sub>150</sub>	Met	His	Arg	Tyr	Gln <sub>155</sub>	Lys	Ala	Ala	Lys	Leu <sub>160</sub>
Phe	Gln	Gly	Lys	Ile <sub>165</sub>	Leu	Phe	Ile	Leu	Val <sub>170</sub>	Asp	Ser	Gly	Met	Lys <sub>175</sub>	Glu
Asn	Gly	Lys	Val <sub>180</sub>	Ile	Ser	Phe	Phe	Lys <sub>185</sub>	Leu	Lys	Glu	Ser	Gln <sub>190</sub>	Leu	Pro
Ala	Leu	Ala <sub>195</sub>	Ile	Tyr	Gln	Thr	Leu	Asp <sub>200</sub>	Asp	Glu	Trp	Asp <sub>205</sub>	Thr	Leu	Pro
Thr	Ala <sub>210</sub>	Glu	Val	Ser	Val	Glu <sub>215</sub>	His	Val	Gln	Asn <sub>220</sub>	Phe	Cys	Asp	Gly	Phe
Leu <sub>225</sub>	Ser	Gly	Lys	Leu	Leu <sub>230</sub>	Lys	Glu	Asn	Arg	Glu <sub>235</sub>	Ser	Glu	Gly	Lys	Thr <sub>240</sub>
Pro	Lys	Val	Glu	Leu <sub>245</sub>											

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<210> 216
<211> 459
<212> PRT
<213> Homo sapiens
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<400>	216														
Met	Phe	Pro	Leu	His	Leu	Ala	Val	Leu	Phe	Gly	Phe	Ser	Asp	Cys	Cys
1				5					10					15	
Arg	Lys	Leu	Leu	Ser	Ser	Gly	Gln	Leu	Tyr	Ser	Ile	Val	Ser	Ser	Leu
			20					25					30		
Ser	Asn	Glu	His	Val	Leu	Ser	Ala	Gly	Phe	Asp	Ile	Asn	Thr	Pro	Asp
		35					40					45			
Asn	Leu	Gly	Arg	Thr	Cys	Leu	His	Ala	Ala	Ala	Ser	Gly	Gly	Asn	Val
50						55					60				
Glu	Cys	Leu	Asn	Leu	Leu	Leu	Ser	Ser	Gly	Ala	Asp	Leu	Arg	Arg	Arg
65					70					75					80
Asp	Lys	Phe	Gly	Arg	Thr	Pro	Leu	His	Tyr	Ala	Ala	Ala	Asn	Gly	Ser
				85					90					95	
Tyr	Gln	Cys	Ala	Val	Thr	Leu	Val	Thr	Ala	Gly	Ala	Gly	Val	Asn	Glu
			100					105					110		
Ala	Asp	Cys	Lys	Gly	Cys	Ser	Pro	Leu	His	Tyr	Ala	Ala	Ala	Ser	Asp
		115					120					125			

Thr Tyr Arg Arg Ala Glu Pro His Thr Pro Ser Ser His Asp Ala Glu  
 130 135 140  
 Glu Asp Glu Pro Leu Lys Glu Ser Arg Arg Lys Glu Ala Phe Phe Cys  
 145 150 155 160  
 Leu Glu Phe Leu Leu Asp Asn Gly Ala Asp Pro Ser Leu Arg Asp Arg  
 165 170 175  
 Gln Gly Tyr Thr Ala Val His Tyr Ala Ala Ala Tyr Gly Asn Arg Gln  
 180 185 190  
 Asn Leu Glu Leu Leu Leu Glu Met Ser Phe Asn Cys Leu Glu Asp Val  
 195 200 205  
 Glu Ser Thr Ile Pro Val Ser Pro Leu His Leu Ala Ala Tyr Asn Gly  
 210 215 220  
 His Cys Glu Ala Leu Lys Thr Leu Ala Glu Thr Leu Val Asn Leu Asp  
 225 230 235 240  
 Val Arg Asp His Lys Gly Arg Thr Ala Leu Phe Leu Ala Thr Glu Arg  
 245 250 255  
 Gly Ser Thr Glu Cys Val Glu Val Leu Thr Ala His Gly Ala Ser Ala  
 260 265 270  
 Leu Ile Lys Glu Arg Lys Arg Lys Trp Thr Pro Leu His Ala Ala Ala  
 275 280 285  
 Ala Ser Gly His Thr Asp Ser Leu His Leu Leu Ile Asp Ser Gly Glu  
 290 295 300  
 Arg Ala Asp Ile Thr Asp Val Met Asp Ala Tyr Gly Gln Thr Pro Leu  
 305 310 315 320  
 Met Leu Ala Ile Met Asn Gly His Val Asp Cys Val His Leu Leu Leu  
 325 330 335  
 Glu Lys Gly Ser Thr Ala Asp Ala Ala Asp Leu Arg Gly Arg Thr Ala  
 340 345 350  
 Leu His Arg Gly Ala Val Thr Gly Cys Glu Asp Cys Leu Ala Ala Leu  
 355 360 365  
 Leu Asp His Asp Ala Phe Val Leu Cys Arg Asp Phe Lys Gly Arg Thr  
 370 375 380  
 Pro Ile His Leu Ala Ser Ala Cys Gly His Thr Ala Val Leu Arg Thr  
 385 390 395 400  
 Leu Leu Gln Ala Ala Leu Ser Thr Asp Pro Leu Asp Ala Gly Val Asp  
 405 410 415  
 Tyr Ser Gly Tyr Ser Pro Met His Trp Ala Ser Tyr Thr Gly His Glu  
 420 425 430  
 Asp Cys Leu Glu Leu Leu Leu Glu His Ser Pro Phe Ser Tyr Leu Glu  
 435 440 445  
 Gly Asn Pro Phe Thr Pro Ser Leu Cys Ser Asp  
 450 455

120

<210> 217  
 <211> 110  
 <212> PRT  
 <213> Homo sapiens

<400> 217  
 Met Lys Arg Tyr Ile Ile Ser Leu Gln Ser Pro Leu Ser His Ser Ser  
   1                  5                  10                  15  
 Met Trp Pro Ala Tyr Leu Leu Pro Ile Met Leu Leu Ile His Leu Gln  
                   20                  25                  30  
 Ala Ile Cys His Gln Ile Lys Lys Gln Gln Thr Glu Gly Gln Ser Gln  
                   35                  40                  45  
 Asp Val Leu Thr His His Cys Asn Phe Leu Leu Glu Met Ile Pro Phe  
                   50                  55                  60  
 Arg Lys Arg Leu Val Glu Ile Gly Val Lys Gly Thr Leu Gln Ile Ser  
   65                  70                  75                  80  
 Pro Val Leu Ser Tyr Phe Gln Leu Tyr Arg Gln Glu Gln Phe Lys Ser  
                   85                  90                  95  
 Lys Glu Phe Ser Arg Phe Leu Gln Cys His Lys Ala Val Ser  
                   100                  105                  110

<210> 218  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 218  
 Met Pro Pro Pro Phe Leu Arg Lys Pro Leu Ile Leu Cys Val Phe Leu  
   1                  5                  10                  15  
 Pro Thr Glu Gly Asn Cys Gly Gly Ser Ser Leu Ala Phe Leu Leu Asn  
                   20                  25                  30  
 Phe Ala Gly Asn Ser Pro Gln Phe Leu Ser Glu Val Arg Thr Val His  
                   35                  40                  45  
 Tyr Gln Arg Asp Trp Thr Leu Tyr Pro Leu Ala Lys Trp Glu Lys Ile  
   50                  55                  60  
 Leu Pro Ala His Ser Thr Pro Pro Trp Pro Ser Pro Thr Pro His Pro  
   65                  70                  75                  80  
 Gln Gln His Phe His Gly Asn Pro Asp Gly Arg Val Val Leu Trp Leu  
                   85                  90                  95  
 Ser Cys Asp Arg Leu Ala Phe Ile Leu Glu Ser  
                   100                  105

<210> 219  
 <211> 428  
 <212> PRT  
 <213> Homo sapiens

<400> 219  
 Met Gly Pro Pro Pro Gly Ala Gly Val Ser Cys Arg Gly Gly Cys Gly  
   1                  5                  10                  15



Phe Ser Arg Leu Leu Ala Trp Cys Phe Leu Leu Ala Leu Ser Pro Gln  
                     20                    25                    30  
 Ala Pro Gly Ser Arg Gly Ala Glu Ala Val Trp Thr Ala Tyr Leu Asn  
                     35                    40                    45  
 Val Ser Trp Arg Val Pro His Thr Gly Val Asn Arg Thr Val Trp Glu  
                     50                    55                    60  
 Leu Ser Glu Glu Gly Val Tyr Gly Gln Asp Ser Pro Leu Glu Pro Val  
                     65                    70                    75                    80  
 Ala Gly Val Leu Val Pro Pro Asp Gly Pro Gly Ala Leu Asn Ala Cys  
                     85                    90                    95  
 Asn Pro His Thr Asn Phe Thr Val Pro Thr Val Trp Gly Ser Thr Val  
                     100                    105                    110  
 Gln Val Ser Trp Leu Ala Leu Ile Gln Arg Gly Gly Gly Cys Thr Phe  
                     115                    120                    125  
 Ala Asp Lys Ile His Leu Ala Tyr Glu Arg Gly Ala Ser Gly Ala Val  
                     130                    135                    140  
 Ile Phe Asn Phe Pro Gly Thr Arg Asn Glu Val Ile Pro Met Ser His  
                     145                    150                    155                    160  
 Pro Gly Ala Val Asp Ile Val Ala Ile Met Ile Gly Asn Leu Lys Gly  
                     165                    170                    175  
 Thr Lys Ile Leu Gln Ser Ile Gln Arg Gly Ile Gln Val Thr Met Val  
                     180                    185                    190  
 Ile Glu Val Gly Lys Lys His Gly Pro Trp Val Asn His Tyr Ser Ile  
                     195                    200                    205  
 Phe Phe Val Ser Val Ser Phe Phe Ile Ile Thr Ala Ala Thr Val Gly  
                     210                    215                    220  
 Tyr Phe Ile Phe Tyr Ser Ala Arg Arg Leu Arg Asn Ala Arg Ala Gln  
                     225                    230                    235                    240  
 Ser Arg Lys Gln Arg Gln Leu Lys Ala Asp Ala Lys Lys Ala Ile Gly  
                     245                    250                    255  
 Arg Leu Gln Leu Arg Thr Leu Lys Gln Gly Asp Lys Glu Ile Gly Pro  
                     260                    265                    270  
 Asp Gly Asp Ser Cys Ala Val Cys Ile Glu Leu Tyr Lys Pro Asn Asp  
                     275                    280                    285  
 Leu Val Arg Ile Leu Thr Cys Asn His Ile Phe His Lys Thr Cys Val  
                     290                    295                    300  
 Asp Pro Trp Leu Leu Glu His Arg Thr Cys Pro Met Cys Lys Cys Asp  
                     305                    310                    315                    320  
 Ile Leu Lys Ala Leu Gly Ile Glu Val Asp Val Glu Asp Gly Ser Val  
                     325                    330                    335  
 Ser Leu Gln Val Pro Val Ser Asn Glu Ile Ser Asn Ser Ala Ser Ser  
                     340                    345                    350  
 His Glu Glu Asp Asn Arg Ser Glu Thr Ala Ser Ser Gly Tyr Ala Ser  
                     355                    360                    365

122

Val Gln Gly Thr Asp Glu Pro Pro Leu Glu Glu His Val Gln Ser Thr  
 370 375 380

Asn Glu Ser Leu Gln Leu Val Asn His Glu Ala Asn Ser Val Ala Val  
 385 390 395 400

Asp Val Ile Pro His Val Asp Asn Pro Thr Phe Glu Glu Asp Glu Thr  
 405 410 415

Pro Asn Gln Glu Thr Ala Val Arg Glu Ile Lys Ser  
 420 425

<210> 220  
 <211> 124  
 <212> PRT  
 <213> Homo sapiens

<400> 220  
 Met Leu Thr Gln Ser Gln Gln Val Leu Arg Gly Ile Leu Leu Phe Leu  
 1 5 10 15

Gln Asn Ile Leu Gln Val Ser Trp Gly Ser Pro Leu Ala Leu Ala Ser  
 20 25 30

Pro Pro Ser Pro Ser Leu Gln Pro Gly Asn Gly Leu Ala Ser Ser Leu  
 35 40 45

Leu Ala Leu Gln Pro Gly Leu Ala Gly Pro Trp Ala Gly Pro Gln Glu  
 50 55 60

Pro Ser Pro Ala Met Cys Phe Pro Lys Lys Arg Ser Leu Trp Pro Asn  
 65 70 75 80

Leu Arg Lys Gln Trp Ala Ser Ile His Ile Asn Asp Pro Arg Gly Thr  
 85 90 95

Leu Cys Pro Arg Cys Thr Gly Cys Asn Gln Arg Gly Ser Gly Gly Ser  
 100 105 110

Gly Leu Ile Trp Arg Asp Arg Phe Tyr His His Pro  
 115 120

<210> 221  
 <211> 87  
 <212> PRT  
 <213> Homo sapiens

<400> 221  
 Met Thr Trp Ser Phe Cys Phe Ala Leu Phe Cys Phe Val Leu Phe Phe  
 1 5 10 15

Ala Ala Ser Leu Ile Gly Tyr Ile Leu Leu Pro Ser Ala Ser Pro Arg  
 20 25 30

Asn His Arg Arg Pro Asn Asn Glu Ala Arg Val Gly Thr Pro Gly Gln  
 35 40 45

Leu Asp Asp Glu Leu Lys Gly Arg Gln Pro Leu Ala Ser Arg Leu Glu  
 50 55 60

Thr Ser Gln Cys Thr Gln Gly Leu Leu Ala Ser Arg Pro Ser Gly Val

123

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65                               75                               80
Ser Lys Ala Leu Leu Tyr Pro
                        85

<210> 222
<211> 84
<212> PRT
<213> Homo sapiens

<400> 222
Met Glu Trp Gln Phe Gly Lys Pro Ser Phe Leu Leu Ser Leu Leu Met
  1                               5                               10                               15

Leu Leu Val Leu Glu Trp Lys Ala Leu Cys Gly Val Arg Leu Gly His
                20                               25                               30

Leu Gly Leu Gln Val Pro Asn Pro Ser Leu Lys Ser Thr Cys Leu Trp
    35                               40                               45

Pro Leu Arg Ser Leu Cys Pro Trp Arg Leu Tyr Pro Ile Lys Ile Met
    50                               55                               60

Ile Ser Leu Pro Leu Pro Ser Leu Gln Leu Pro Ser Ser Pro His Arg
  65                               70                               75                               80

Pro Phe Gln Leu

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<210> 223
<211> 76
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (43)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 223
Met  Pro  Leu  Pro  Pro  Lys  Trp  Pro  Pro  Leu  Leu  Thr  Ala  Leu  Leu  Cys
 1          5          10          15

His  Leu  Leu  Ser  Thr  Ser  Ser  Pro  Leu  Leu  Ile  Ile  Leu  Pro  Asn  His
          20          25          30

Arg  Ser  Asp  His  Pro  Leu  Thr  Asp  Leu  Ser  Xaa  Leu  Ser  Ile  Ala  Tyr
          35          40          45

Lys  Asn  Glu  Asn  Gln  Thr  Thr  Glu  Leu  Ser  Met  Thr  Val  Lys  Ala  Leu
          50          55          60

His  Leu  Ala  Ser  Ile  Tyr  Cys  Ile  Leu  His  Ala  Ser
          65          70          75

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<210> 224
<211> 142
<212> PRT
<213> Homo sapiens
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124

&lt;400&gt; 224

```

Met Leu Trp Thr Thr Leu Thr Gly Val Ser Leu Ala Leu Phe Pro Val
 1           5           10           15

Ala Gln Ala Pro Thr Ala Leu Val Ala Leu Ala Val Ala Tyr Gly Phe
          20           25           30

Thr Ser Gly Ala Leu Ala Pro Leu Ala Phe Ser Val Leu Pro Glu Leu
          35           40           45

Ile Gly Thr Arg Arg Ile Tyr Cys Gly Leu Gly Leu Leu Gln Met Ile
          50           55           60

Glu Ser Ile Gly Gly Leu Leu Gly Pro Pro Leu Ser Gly Tyr Leu Arg
          65           70           75           80

Asp Val Thr Gly Asn Tyr Thr Ala Ser Phe Val Val Ala Gly Ala Phe
          85           90           95

Leu Leu Ser Gly Ser Gly Ile Leu Leu Thr Leu Pro His Phe Phe Cys
          100          105          110

Phe Ser Thr Thr Thr Ser Gly Pro Gln Asp Leu Val Thr Glu Ala Leu
          115          120          125

Asp Thr Lys Val Pro Leu Pro Lys Glu Gly Leu Glu Glu Asp
          130          135          140

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&lt;210&gt; 225

&lt;211&gt; 84

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 225

```

Met Phe Leu Ser Gly Lys Pro Gly Glu Ser Tyr Leu Ser His Leu Pro
 1           5           10           15

Cys Leu Phe Phe Phe Phe Phe Phe Gly Trp Ser Cys Cys Leu Asp
          20           25           30

Asp Ala Phe Thr Met Gln Glu Arg Val Phe Val Lys Asp Ile Phe Glu
          35           40           45

Asp Trp Leu Phe His Ile Val Leu His Ser Leu Thr Val Ala Lys Cys
          50           55           60

Thr Val Asp Phe His Asp His Cys Ile Phe Leu Val Ile Glu Met Tyr
          65           70           75           80

Leu Leu Cys Phe

```

&lt;210&gt; 226

&lt;211&gt; 88

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 226

```

Met Phe Pro Ile Leu Ser Ile Thr Thr Leu Ser Ile Leu Ala Phe Phe
 1           5           10           15

Leu Trp Leu Ser Val Thr Ser His Phe Tyr Arg Gln Lys Thr Gly Phe

```

125

	20		25		30										
His	His	Ser	Pro	Ser	Phe	Tyr	Leu	Ile	Val	Gln	Ile	Trp	Asp	Thr	Tyr
		35					40					45			
Ala	Asp	Ile	Val	Ala	Ser	Glu	Tyr	Val	Phe	Pro	Trp	Arg	Lys	Thr	Leu
	50					55					60				
Ser	Ser	Arg	Glu	Gln	Cys	Leu	Ser	Val	Val	Pro	Val	Ala	Phe	Ser	Leu
65					70					75					80
Ile	Asp	Phe	Ile	Ser	Lys	Val	Ser								
				85											

<210> 227  
 <211> 127  
 <212> PRT  
 <213> Homo sapiens

<400> 227															
Met	Met	Pro	Thr	Tyr	Ala	Ile	Cys	Met	Val	Leu	Val	Phe	Leu	Leu	Leu
1				5					10					15	
Val	His	Leu	His	Ile	Ile	Asn	Thr	Asn	Thr	His	Thr	His	Thr	His	Thr
			20					25					30		
His	Thr	His	Thr	Gly	Leu	Leu	Pro	Glu	Pro	Tyr	Met	Leu	Tyr	Phe	Gln
			35				40					45			
Phe	Leu	Ser	Val	Leu	Arg	Gly	Tyr	Ile	Leu	Ser	Arg	Trp	Thr	Asp	Arg
	50					55					60				
Glu	Tyr	Thr	Trp	Ile	Ser	Thr	Lys	Ile	Tyr	Ser	Pro	Asn	Ser	Pro	Glu
65					70					75					80
Pro	Pro	Ala	Ser	Cys	Pro	Ser	Pro	Thr	Gln	Ser	Ile	Ser	Arg	His	Ala
				85					90					95	
Val	Gln	Gly	Ser	Thr	Phe	Leu	Lys	Ala	Gln	Leu	Pro	Thr	Ser	Glu	Gln
			100					105					110		
Val	Gln	Ile	His	Pro	Leu	His	Pro	Pro	Ile	His	Leu	Ser	Pro	Leu	
		115					120					125			

<210> 228  
 <211> 83  
 <212> PRT  
 <213> Homo sapiens

<400> 228															
Met	Thr	Ser	Leu	Ala	Arg	Leu	Pro	Cys	Ser	Tyr	Leu	Cys	Leu	Pro	Cys
1				5					10					15	
Gln	Leu	Ser	Ser	Cys	Cys	Ala	Phe	Ser	Gln	Pro	Ile	Ser	Ala	Leu	Leu
			20					25					30		
Pro	Ser	Pro	Ser	Thr	Pro	Val	Leu	Leu	Ser	Ala	Pro	Arg	Pro	Ser	Ser
		35					40					45			
Gln	Gly	Val	Pro	Gly	Thr	Arg	Ser	Glu	Phe	Pro	Ser	Thr	Pro	Phe	Cys
	50					55					60				

126

Leu Pro Ser Phe Pro Arg Glu Ser Phe Leu Asp Ser Phe His Leu Val  
 65 70 75 80

Ser Ser His

<210> 229  
 <211> 114  
 <212> PRT  
 <213> Homo sapiens

<400> 229  
 Met Ala Lys Ala Pro Phe Tyr His Leu Leu Phe Cys Phe Gly Ile Trp  
 1 5 10 15  
 Ser Asp Ser Tyr Ser Ser Leu Gly Leu Ala Gln Trp Arg Asn Trp Cys  
 20 25 30  
 Ser Tyr Cys Thr Gly Leu Cys Thr Pro Cys Asn Cys Asp Val Tyr Asp  
 35 40 45  
 Cys Ser Ser Cys Phe Pro Ile Leu His Phe Gln Ser Pro Arg Ala Val  
 50 55 60  
 Leu Ser Arg Ile Thr Ser Thr Val Asn Gln Arg Arg Asp Cys Thr Thr  
 65 70 75 80  
 Arg His Val Cys Trp Glu Arg Arg Lys Gly Glu Lys Pro Trp Pro Lys  
 85 90 95  
 Gln Ser Ile Pro Gln Ile Leu Arg His Ser Phe Val Tyr Leu Val Phe  
 100 105 110  
 His His

<210> 230  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<400> 230  
 Met Arg Trp Arg Lys Pro Leu Cys Leu Trp Cys Leu Leu Thr Gln Gly  
 1 5 10 15  
 Glu Thr Glu Ala Gln Ala Gly Gln Pro Leu Ala Trp Gly Gly Gly Trp  
 20 25 30  
 Val Val Leu Arg Pro Val Thr Ser Pro Leu Gln His Pro Pro Val Asp  
 35 40 45  
 Pro Leu Pro Ala Pro Ala Arg Pro Glu Ser Cys Ser Gln Ala Gln Thr  
 50 55 60  
 Leu Ala Cys Pro Ser Gly Asp Ala Gly Gln Tyr Ser Ser Leu Gln Pro  
 65 70 75 80  
 Ser

127

<210> 231  
 <211> 273  
 <212> PRT  
 <213> Homo sapiens

<400> 231  
 Met Thr Ser Gly Pro Arg Gly Val Val His Phe Tyr Gly Tyr Ser Val  
           1                          5                          10                          15  
 Val Ser Thr Leu Ala Leu Leu Val Ser Ile Ala Phe Pro Ile Pro Ile  
                           20                          25                          30  
 Cys Gln Gln Trp Glu Pro Ser Tyr Lys Arg Val Lys Ala Leu Ser Ile  
                           35                          40                          45  
 Val Gly Gly Asp Pro His Leu Ile Leu Leu Ala Ser Thr Thr Val Leu  
           50                          55                          60  
 Val Gly Ala Ile Val Ser Thr Val Gln Asn Phe Leu Phe Trp His Met  
           65                          70                          75                          80  
 Lys Asp His Gly Ser Gly Glu Leu Val Met Gly Phe Ser Val Ala Leu  
                           85                          90                          95  
 Ser Leu Leu Gly Glu Ile Leu Leu His Pro Phe Lys Ala Thr Leu Leu  
                           100                          105                          110  
 Arg Lys Leu Ser Arg Thr Gly Leu Val Gly Leu Gly Leu Ser Cys Leu  
           115                          120                          125  
 Ala Gly Gln Leu Leu Tyr Tyr Ser Phe Leu Trp Ser Trp Trp Ser Val  
           130                          135                          140  
 Leu Pro Ile Gln Ile Leu Ser Ala Ile Ser Asn Arg Ala Leu Trp Trp  
           145                          150                          155                          160  
 Ala Val Gly Ala Ser Val Glu Asp Leu Ala Thr Pro Arg Met Glu Arg  
                           165                          170                          175  
 Ala Leu Ser Ala Leu Phe Arg Gly His Phe Tyr Gly Ser Gly Cys Ser  
           180                          185                          190  
 Leu Gly Ser Phe Val Gly Gly Phe Val Val Met Arg Phe Ser Leu Ala  
           195                          200                          205  
 Val Leu Tyr Gln Ala Cys Cys Val Ala Leu Leu Leu Trp Leu Ala Leu  
           210                          215                          220  
 Leu Leu Ser Ile Gln Arg Arg Leu Pro Arg Glu Arg Lys Ile Lys Tyr  
           225                          230                          235                          240  
 Ser Lys Leu Leu Ser Met Glu Val Ser Asp Thr Ser Asp Ser Glu Gln  
                           245                          250                          255  
 Gly Thr Glu Gln Asp Trp Leu Val Lys Ala Met Arg Glu Glu His Ser  
           260                          265                          270

Asp

<210> 232  
 <211> 112  
 <212> PRT  
 <213> Homo sapiens

128

&lt;400&gt; 232

Met Ala Ser Pro Ala Pro Ala Cys Leu Gly Ser Leu Leu Ser Trp Thr  
 1 5 10 15  
 Val Cys Gly Trp Gly Glu Val Val Ser Gly Pro Pro Cys Ala Val Ser  
 20 25 30  
 Ala Trp Gly Cys Ser Trp Ala Thr Trp Val Thr Pro Ser Val Val Val  
 35 40 45  
 Gln Leu Ala Pro Ser Gly Ala Val Gln Thr Pro Leu Ser Pro Glu Leu  
 50 55 60  
 Leu Val Ile Ser Phe Gln Leu His Ala Ala Pro Leu Gly Gln Phe Tyr  
 65 70 75 80  
 Phe Pro Ile Leu Gln Met Gly Lys Glu Lys Leu Arg Leu Arg Asn Met  
 85 90 95  
 Pro Lys Glu Ala Pro Val Pro Val Phe Cys Phe Val Leu Phe Cys Phe  
 100 105 110

&lt;210&gt; 233

&lt;211&gt; 82

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 233

Met Gly Gln Leu Cys His Ser Pro Ser Cys Leu Pro Ser Gly Ala Phe  
 1 5 10 15  
 Cys Leu Leu Leu Ser Ser Val Leu Gly Ile Ile Val Leu Asn Ser Thr  
 20 25 30  
 Asp Thr Ile Ser Ser Ser His Pro Pro Leu Ser Ser Asn Leu Pro Ser  
 35 40 45  
 Trp Gly Tyr Thr Thr Thr Lys Ala His Leu Ser Leu Gly Leu Val Gly  
 50 55 60  
 Phe Ala Gly Lys Glu Asn Met Lys Glu Leu Tyr Val Glu Ser Ser Arg  
 65 70 75 80  
 Ser Phe

&lt;210&gt; 234

&lt;211&gt; 136

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 234

Met Ile Glu Asp Thr Met Thr Leu Leu Ser Leu Leu Gly Arg Ile Met  
 1 5 10 15  
 Arg Tyr Phe Leu Leu Arg Pro Glu Thr Leu Phe Leu Leu Cys Ile Ser  
 20 25 30



129

Leu Ala Leu Trp Ser Tyr Phe Phe His Thr Asp Glu Val Lys Thr Ile  
           35                                  40                                  45  
 Val Lys Ser Ser Arg Asp Ala Val Lys Met Val Lys Gly Lys Val Ala  
           50                                  55                                  60  
 Glu Ile Met Gln Asn Asp Arg Leu Gly Gly Leu Asp Val Leu Glu Ala  
   65                                  70                                  75                                  80  
 Glu Phe Ser Lys Thr Trp Glu Phe Lys Asn His Asn Val Gly Gly Val  
                                   85                                  90                                  95  
 Leu His Pro Gly Pro Glu Arg Pro His Gly Gly Pro Leu Arg Ser Ser  
                   100                                  105                                  110  
 His Gly Ser Gly Gln Gln Asp Ala Pro Val His Leu Arg Asp Leu Arg  
           115                                  120                                  125  
 Arg Ala Arg Gly Arg Asp Cys Ser  
   130                                  135

<210> 235  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<400> 235  
 Met Lys Ser Lys Phe Cys Phe Ala Ser Pro Met Arg Leu Pro Lys Ala  
   1                                  5                                  10                                  15  
 Leu Leu Ala Phe Ser Ala Cys Trp Gln Leu Leu Ser Ala Trp Leu Leu  
                   20                                  25                                  30  
 Thr Phe Leu Pro Thr Leu Leu Thr Asn Gln Lys Lys Ser Gln Glu  
           35                                  40                                  45

<210> 236  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (58)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (99)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (106)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 236  
 Met Phe Tyr Leu Thr His Pro Ile Lys Asn Phe Asn Met Ser Ser Arg  
   1                                  5                                  10                                  15  
 Lys Lys Lys Cys Ala Phe Tyr Ile Ile Leu Leu Leu Leu Ser Leu Ser  
           20                                  25                                  30

130

Pro Gly Thr Trp Phe Thr Pro Thr Pro Thr Pro Gln Leu Thr Leu Ala  
                   35                                  40                                  45

Val Trp Gln Val Pro Ser Gly His Leu Xaa Arg Ala Leu Cys Ile Gln  
           50                                  55                                  60

Cys Cys Pro Pro Ala Val Ala Gly Ala Val Gly Ala Ser Asp Lys Met  
       65                                  70                                  75                                  80

His Pro Gln Pro Trp Gln Cys Leu Gln Ser Cys Pro Phe Val Asn Ser  
                                   85                                  90                                  95

Gly Pro Xaa His Pro His Ala Arg Pro Xaa Thr Ala Trp Asp Ala Cys  
                   100                                  105                                  110

Ala Gly Gly Arg Ala Phe Leu Val Arg His  
       115                                  120

<210> 237  
 <211> 90  
 <212> PRT  
 <213> Homo sapiens

<400> 237  
 Met Trp Phe Lys Gly Gln Leu His Phe Phe Phe Leu Phe Phe Ser Phe  
       1                                  5                                  10                                  15

Leu Thr Phe Leu Phe Ser Ser Leu Phe Ser Ser Leu Leu Phe Leu Ser  
                   20                                  25                                  30

Phe Leu Phe Phe Pro Phe Phe Leu Ser Gln Gly Phe Ile Leu Ser His  
           35                                  40                                  45

Arg Leu Glu Tyr Asn Gly Ile Gly Ser Leu Gln Pro Gln Thr Pro Arg  
       50                                  55                                  60

Leu Lys Pro Ser Ser Gly Leu Ser Leu Leu Ser Ser Trp Asp Tyr Arg  
       65                                  70                                  75                                  80

Cys Ala Pro Leu Pro His Ser Ala Asn Phe  
                                   85                                  90

<210> 238  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<400> 238  
 Met Pro Asn Ser Leu Leu Gly Val Phe Phe Cys Phe Val Leu Phe Cys  
       1                                  5                                  10                                  15

Phe Val Leu Phe Cys Leu Ile Gln Ser Phe Thr Leu Ser Pro Arg Leu  
                   20                                  25                                  30

Glu

<210> 239  
 <211> 35

131

<212> PRT  
 <213> Homo sapiens

<400> 239  
 Met Cys His His Ala Gln Leu Ile Phe Val Leu Leu Val Glu Thr Gly  
   1                  5                  10                  15  
 Phe Cys His Val Gly Gln Ala Gly Leu Glu Leu Leu Thr Ser His Asp  
                   20                  25                  30  
 Leu Arg Thr  
           35

<210> 240  
 <211> 82  
 <212> PRT  
 <213> Homo sapiens

<400> 240  
 Met Leu Thr Asn Arg Ala Pro Ser Ser Phe Val Trp Phe Leu Cys Leu  
   1                  5                  10                  15  
 Ala Cys His Leu Pro Ser Cys Pro Ser Ala Thr Glu Glu Phe Ala Val  
                   20                  25                  30  
 Phe Ile Pro Lys Tyr His Ser Ser Arg Met Gly Ala Ala Pro Cys His  
           35                  40                  45  
 Val Leu Gly His Gly Gly Ile Lys Gly Asn Thr Cys Gln Asp Asn Ala  
   50                  55                  60  
 Gly Tyr Asp Phe Cys Arg Pro Leu Gly Leu Ala Ser Phe Leu Lys Arg  
   65                  70                  75                  80  
 Gln Asp

<210> 241  
 <211> 219  
 <212> PRT  
 <213> Homo sapiens

<400> 241  
 Met Arg Pro Arg Gly Leu Pro Pro Leu Leu Val Val Leu Leu Gly Cys  
   1                  5                  10                  15  
 Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr  
           20                  25                  30  
 Glu Gly Leu Asn Ser Thr Glu Ala Ala Leu Ala Thr Phe Gly Thr Phe  
   35                  40                  45  
 Pro Ser Thr Arg Pro Pro Gly Thr Pro Arg Ala Pro Gly Pro Ser Ser  
   50                  55                  60  
 Gly Pro Arg Pro Thr Pro Val Thr Asp Val Ala Val Leu Cys Val Cys  
   65                  70                  75                  80  
 Asp Leu Ser Pro Ala Gln Cys Asp Ile Asn Cys Cys Cys Asp Pro Asp  
           85                  90                  95  
 Cys Ser Ser Val Asp Phe Ser Val Phe Ser Ala Cys Ser Val Pro Val

132

		100						105					110				
Val	Thr	Gly	Asp	Ser	Gln	Phe	Cys	Ser	Gln	Lys	Ala	Val	Ile	Tyr	Ser		
		115					120					125					
Leu	Asn	Phe	Thr	Ala	Asn	Pro	Pro	Gln	Arg	Val	Phe	Glu	Leu	Val	Asp		
		130				135					140						
Gln	Ile	Asn	Pro	Ser	Ile	Phe	Cys	Ile	His	Ile	Thr	Asn	Tyr	Lys	Pro		
		145			150					155					160		
Ala	Leu	Ser	Phe	Ile	Asn	Pro	Glu	Val	Pro	Asp	Glu	Asn	Asn	Phe	Asp		
				165					170					175			
Thr	Leu	Met	Lys	Thr	Ser	Asp	Gly	Phe	Thr	Leu	Asn	Ala	Glu	Tyr	Met		
			180					185					190				
Phe	Pro	Ser	Gln	Pro	Asn	Trp	Ile	Phe	Leu	Leu	Leu	Leu	Asn	Met	Ser		
		195					200						205				
Met	Gly	Phe	Leu	Cys	Arg	Leu	Gln	Ile	Arg	Phe							
	210					215											

<210> 242  
 <211> 181  
 <212> PRT  
 <213> Homo sapiens

<400> 242  
 Met Gly Leu Ile Val Val Leu Leu Phe Pro Asn Leu Cys Met Cys Thr  
 1 5 10 15  
 Phe His Ala Gly Gly Phe Gln Cys Val Leu Trp Met Ala Gly Leu Lys  
 20 25 30  
 Arg Arg Val Pro Leu His Ser Leu Arg Tyr Phe Ile Ser Met Val Gly  
 35 40 45  
 Leu Phe Ser Lys Pro Gly Leu Leu Pro Trp Tyr Ala Arg Asn Pro Pro  
 50 55 60  
 Gly Trp Ser Gln Leu Phe Leu Gly Thr Val Cys Lys Gly Asp Phe Thr  
 65 70 75 80  
 Arg Val Ile Ala Thr Lys Cys Gln Lys Gly Gln Lys Ser Gln Lys Lys  
 85 90 95  
 Pro Ser His Leu Gly Pro Leu Asp Gly Ser Trp Gln Glu Arg Leu Ala  
 100 105 110  
 Asp Val Val Thr Pro Leu Trp Arg Leu Ser Tyr Glu Glu Gln Leu Lys  
 115 120 125  
 Val Lys Phe Ala Ala Gln Lys Lys Ile Leu Gln Arg Leu Glu Ser Tyr  
 130 135 140  
 Ile Gln Met Leu Asn Gly Val Ser Val Thr Thr Ala Val Pro Lys Ser  
 145 150 155 160  
 Glu Arg Leu Ser Cys Leu Leu His Pro Ile Ile Pro Leu Ser Cys His  
 165 170 175  
 Gln Trp Leu Pro Lys  
 180

<210> 243  
 <211> 125  
 <212> PRT  
 <213> Homo sapiens

<400> 243  
 Met Ser Asn Thr Asn Gly Ser Ala Ile Thr Glu Phe Ile Leu Leu Gly  
   1                  5                  10                  15  
 Leu Thr Asp Cys Pro Glu Leu Gln Ser Leu Leu Phe Val Leu Phe Leu  
                   20                  25                  30  
 Val Val Tyr Leu Val Thr Leu Leu Gly Asn Leu Gly Met Ile Met Leu  
           35                  40                  45  
 Met Arg Leu Asp Ser Arg Leu His Thr Pro Met Tyr Phe Phe Leu Thr  
       50                  55                  60  
 Asn Leu Ala Phe Val Asp Leu Cys Tyr Thr Ser Asn Ala Thr Pro Gln  
   65                  70                  75                  80  
 Met Ser Thr Asn Ile Val Ser Glu Lys Thr Ile Ser Phe Ala Gly Cys  
                   85                  90                  95  
 Phe Thr Gln Cys Tyr Ile Phe Ile Ala Leu Leu Leu Thr Glu Phe Tyr  
           100                  105                  110  
 Met Leu Ala Ala Met Ala Tyr Asp Arg Tyr Val Ala Ile  
       115                  120                  125

<210> 244  
 <211> 132  
 <212> PRT  
 <213> Homo sapiens

<400> 244  
 Met Arg Leu Leu Val Leu Ser Ser Leu Leu Cys Ile Leu Leu Leu Cys  
   1                  5                  10                  15  
 Phe Ser Ile Phe Ser Thr Glu Gly Lys Arg Arg Pro Ala Lys Ala Trp  
           20                  25                  30  
 Ser Gly Arg Arg Thr Arg Leu Cys Cys His Arg Val Pro Ser Pro Asn  
       35                  40                  45  
 Ser Thr Asn Leu Lys Ala Phe Thr Ala Val Ser Cys Asn Val Gly Gly  
       50                  55                  60  
 Leu His Leu Gly Leu Gln Gly Pro Trp Glu Ser Ser Arg Thr Pro Arg  
   65                  70                  75                  80  
 Pro Cys Leu Asn Cys Ala Ile Asn Phe Gln Ser Tyr His Glu Pro Thr  
                   85                  90                  95  
 Ser Pro His Arg Ala Ser Val Ala Thr Met Trp Ala Ser Pro Val Gln  
       100                  105                  110  
 Thr Thr Glu His Ser Thr Met Thr Gly His Ser Tyr Lys Ser Arg Asp  
       115                  120                  125  
 His Gln Ser Cys

134

130

&lt;210&gt; 245

&lt;211&gt; 186

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 245

Met Ser Gly Leu Ser Arg Pro Leu Leu Leu Ala Val Gly Cys Leu Ala  
 1 5 10 15

Ala Leu Cys Val Ile Thr Ala Ala Gly Asn Thr Thr Leu Ala Pro Asn  
 20 25 30

Val Thr Thr Ala Ser Ser Pro Pro Pro Thr Thr Thr Thr Val Pro Val  
 35 40 45

Ser Pro Thr Thr Leu Ser Pro Leu Pro Val Thr Thr Pro Ala Pro Asp  
 50 55 60

Ile Cys Gly Ser Arg Asn Ser Cys Val Ser Cys Val Asp Gly Asn Ala  
 65 70 75 80

Thr Cys Phe Trp Ile Glu Cys Lys Gly Lys Ser Tyr Cys Ser Asp Asn  
 85 90 95

Ser Thr Ala Gly Asp Cys Lys Val Val Asn Thr Thr Gly Phe Cys Ser  
 100 105 110

Ala Lys Thr Thr Thr Leu Pro Ser Thr Thr Thr Thr Ser Thr Thr Ala  
 115 120 125

Thr Thr Ser Gly Thr Thr Asn Thr Thr Leu Ser Pro Thr Ile Gln Pro  
 130 135 140

Thr Arg Lys Ser Thr Phe Asp Ala Ala Ser Phe Ile Gly Gly Ile Val  
 145 150 155 160

Leu Val Leu Gly Val Gln Ala Val Ile Phe Phe Leu Tyr Lys Phe Cys  
 165 170 175

Lys Ser Lys Glu Arg Asn Tyr His Thr Leu  
 180 185

&lt;210&gt; 246

&lt;211&gt; 114

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 246

Met Leu Val Pro Ala Ala Leu Thr Gly Leu Leu Val Phe Leu Ser Gly  
 1 5 10 15

Phe Ser Leu Phe Glu Ala Ser Gln Ile Ser Lys Glu Ile Cys Glu Ala  
 20 25 30

His Asp Ile Leu Met Cys Pro Leu Gly Asp His Ser Arg Arg Tyr Gln  
 35 40 45

Arg Leu Ser Glu Thr Cys Thr Phe Ala Lys Leu Thr His Leu Phe Asp  
 50 55 60

135

Asn Asp Gly Thr Val Val Phe Ala Ile Phe Met Ala Leu Trp Ala Thr  
 65 70 75 80

Val Phe Leu Glu Ile Trp Lys Arg Gln Arg Ala Arg Val Val Leu His  
 85 90 95

Trp Asp Leu Tyr Val Trp Asp Glu Glu Gln Val Arg Trp Ser Trp Gln  
 100 105 110

Arg Ser

<210> 247  
 <211> 91  
 <212> PRT  
 <213> Homo sapiens

<400> 247  
 Met Ser Arg Cys Thr Trp Pro Ser Phe Ser Phe Phe Leu Ser Ser Phe  
 1 5 10 15

Leu Ser Phe Phe Arg Trp Ser Leu Ala Leu Ser Ala Arg Leu Glu Gly  
 20 25 30

Ser Gly Val Ile Leu Ala His Cys Asn Leu Arg Leu Pro Gly Ser Ser  
 35 40 45

Asp Ser Pro Ala Ser Ala Ser Gln Ser Ala Gly Ile Thr Gly Met Ser  
 50 55 60

Arg Cys Ala Asp Val His Leu Val Ser Ile Ile Thr Lys Ala His Leu  
 65 70 75 80

Val Ser Trp Pro Leu Gln Met Asn Ile Leu Pro  
 85 90

<210> 248  
 <211> 73  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (33)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (52)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 248  
 Met Val Phe Pro Leu Leu Cys Val Phe Val Leu Ile Ser Ser Ser Leu  
 1 5 10 15

Ala Gly Glu Glu Ala Ala Gly Leu Arg Val Gln Lys Leu Trp Pro Ala  
 20 25 30

136

Xaa Xaa Leu Ser His Leu Pro Val Cys Trp Phe His Cys Ser Gly Ile  
           35                                  40                                  45  
 Trp Ser Glu Xaa Ile Glu Leu Lys Val Gly Trp Glu Gly His Val Leu  
           50                                  55                                  60  
 Pro Trp Gln Ala His Val Val Glu Phe  
           65                                  70

<210> 249  
 <211> 118  
 <212> PRT  
 <213> Homo sapiens

<400> 249  
 Met His Cys His Cys Arg Val Trp Gly Phe Arg Trp Phe Leu Gly Asp  
       1                                  5                                  10                                  15  
 Trp Glu Leu Leu Val Cys Met Cys Trp Val His Ala Ser Gly Ser Gln  
           20                                  25                                  30  
 Leu Pro Gln Ala Arg Thr Gly Asn Pro Phe Pro Ser Lys Ala Ile Gly  
           35                                  40                                  45  
 Gly Ala Ser Leu Glu Ser Phe Ala Lys Ser Pro Arg Gln Asn Pro Arg  
           50                                  55                                  60  
 Val Gln Asp His Phe His Gly Ala His Val Phe Leu Phe Cys Arg Asn  
           65                                  70                                  75                                  80  
 Phe Phe Leu Thr Ser Thr His His Asn Ser Glu Gly His Val Ser Ser  
           85                                  90                                  95  
 Phe Leu Asp His Tyr Ser Glu Val Leu Gln Leu Tyr Ser Ser Gln Ser  
           100                                  105                                  110  
 Gly Leu Gly Leu Leu Gly  
           115

<210> 250  
 <211> 466  
 <212> PRT  
 <213> Homo sapiens

<400> 250  
 Met Phe Gly Thr Leu Leu Leu Tyr Cys Phe Phe Leu Ala Thr Val Pro  
       1                                  5                                  10                                  15  
 Ala Leu Ala Glu Thr Gly Gly Glu Arg Gln Leu Ser Pro Glu Lys Ser  
           20                                  25                                  30  
 Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu Pro Ala Arg  
           35                                  40                                  45  
 Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn Lys Phe Thr Ser  
           50                                  55                                  60  
 Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val Ser Ala Pro Glu Glu  
           65                                  70                                  75                                  80  
 Gln Phe Thr Arg Val Gly Val Gln Val Leu Asp Arg Lys Asp Gly Ser



137

85					90					95					
Phe	Ile	Val	Arg	Tyr	Arg	Met	Tyr	Ala	Ser	Tyr	Lys	Asn	Leu	Lys	Val
			100					105					110		
Glu	Val	Lys	Phe	Gln	Gly	Gln	His	Val	Ala	Lys	Ser	Pro	Tyr	Ile	Leu
		115					120					125			
Lys	Gly	Pro	Val	Tyr	His	Glu	Asn	Cys	Asp	Cys	Pro	Leu	Gln	Asp	Ser
	130					135					140				
Ala	Ala	Trp	Leu	Arg	Glu	Met	Asn	Cys	Pro	Glu	Thr	Ile	Ala	Gln	Ile
145					150					155					160
Gln	Arg	Asp	Leu	Ala	His	Phe	Pro	Ala	Val	Asp	Pro	Glu	Lys	Ile	Ala
				165					170					175	
Val	Glu	Ile	Pro	Lys	Arg	Phe	Gly	Gln	Arg	Gln	Ser	Leu	Cys	His	Tyr
			180					185					190		
Thr	Leu	Lys	Asp	Asn	Lys	Val	Tyr	Ile	Lys	Thr	His	Gly	Glu	His	Val
		195					200					205			
Gly	Phe	Arg	Ile	Phe	Met	Asp	Ala	Ile	Leu	Leu	Ser	Leu	Thr	Arg	Lys
	210					215					220				
Val	Lys	Met	Pro	Asp	Val	Glu	Leu	Phe	Val	Asn	Leu	Gly	Asp	Trp	Pro
225					230					235					240
Leu	Glu	Lys	Lys	Lys	Ser	Asn	Ser	Asn	Ile	His	Pro	Ile	Phe	Ser	Trp
				245					250					255	
Cys	Gly	Ser	Thr	Asp	Ser	Lys	Asp	Ile	Val	Met	Pro	Thr	Tyr	Asp	Leu
			260					265					270		
Thr	Asp	Ser	Val	Leu	Glu	Thr	Met	Gly	Arg	Val	Ser	Leu	Asp	Met	Met
		275					280					285			
Ser	Val	Gln	Ala	Asn	Thr	Gly	Pro	Pro	Trp	Glu	Ser	Lys	Asn	Ser	Thr
	290					295					300				
Ala	Val	Trp	Arg	Gly	Arg	Asp	Ser	Arg	Lys	Glu	Arg	Leu	Glu	Leu	Val
305				310						315					320
Lys	Leu	Ser	Arg	Lys	His	Pro	Glu	Leu	Ile	Asp	Ala	Ala	Phe	Thr	Asn
				325					330					335	
Phe	Phe	Phe	Phe	Lys	His	Asp	Glu	Asn	Leu	Tyr	Gly	Pro	Ile	Val	Lys
			340					345					350		
His	Ile	Ser	Phe	Phe	Asp	Phe	Phe	Lys	His	Lys	Tyr	Gln	Ile	Asn	Ile
		355					360					365			
Asp	Gly	Thr	Val	Ala	Ala	Tyr	Arg	Leu	Pro	Tyr	Leu	Leu	Val	Gly	Asp
	370					375					380				
Ser	Val	Val	Leu	Lys	Gln	Asp	Ser	Ile	Tyr	Tyr	Glu	His	Phe	Tyr	Asn
385					390					395					400
Glu	Leu	Gln	Pro	Trp	Lys	His	Tyr	Ile	Pro	Val	Lys	Ser	Asn	Leu	Ser
				405					410					415	
Asp	Leu	Leu	Glu	Lys	Leu	Lys	Trp	Ala	Lys	Asp	His	Asp	Glu	Glu	Ala
			420					425					430		
Lys	Lys	Ile	Ala	Lys	Ala	Gly	Gln	Glu	Phe	Ala	Arg	Asn	Asn	Leu	Met

138

435                      440                      445  
 Gly Asp Asp Ile Phe Cys Tyr Tyr Phe Lys Leu Phe Gln Thr Lys Asp  
     450                      455                      460  
 Glu Leu  
 465

<210> 251  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<400> 251  
 Met Thr Cys Gln Leu Leu Phe Asn Ser Phe Leu Leu Ser Ser Val Ser  
     1                      5                      10                      15  
 Gln Ile Arg Asp Gln Ile Ala Met Arg Glu Ser Val Trp Ser Gly Ser  
                     20                      25                      30  
 Ile Ser Arg Gln Lys Glu Leu Val Thr Leu Trp Ile Ile Cys Leu Trp  
                     35                      40                      45  
 Phe Arg His Leu Pro Leu Val Leu Ala Val Gly Asp Gly Trp  
                     50                      55                      60

<210> 252  
 <211> 306  
 <212> PRT  
 <213> Homo sapiens

<400> 252  
 Met Gly His Arg Thr Leu Val Leu Pro Trp Val Leu Leu Thr Leu Cys  
     1                      5                      10                      15  
 Val Thr Ala Gly Thr Pro Glu Val Trp Val Gln Val Arg Met Glu Ala  
                     20                      25                      30  
 Thr Glu Leu Ser Ser Phe Thr Ile Arg Cys Gly Phe Leu Gly Ser Gly  
                     35                      40                      45  
 Ser Ile Ser Leu Val Thr Val Ser Trp Gly Gly Pro Asp Gly Ala Gly  
                     50                      55                      60  
 Gly Thr Thr Leu Ala Val Leu His Pro Glu Arg Gly Ile Arg Gln Trp  
     65                      70                      75                      80  
 Ala Pro Ala Arg Gln Ala Arg Trp Glu Thr Gln Ser Ser Ile Ser Leu  
                     85                      90                      95  
 Ile Leu Glu Gly Ser Gly Ala Ser Ser Pro Cys Ala Asn Thr Thr Phe  
                     100                      105                      110  
 Cys Cys Lys Phe Ala Ser Phe Pro Glu Gly Ser Trp Glu Ala Cys Gly  
                     115                      120                      125  
 Ser Leu Pro Pro Ser Ser Asp Pro Gly Leu Ser Ala Pro Pro Thr Pro  
                     130                      135                      140  
 Ala Pro Ile Leu Arg Ala Asp Leu Ala Gly Ile Leu Gly Val Ser Gly  
     145                      150                      155                      160

Val Leu Leu Phe Gly Cys Val Tyr Leu Leu His Leu Leu Arg Arg His  
 165 170 175  
 Lys His Arg Pro Ala Pro Arg Leu Gln Pro Ser Arg Thr Ser Pro Gln  
 180 185 190  
 Ala Pro Arg Ala Arg Ala Trp Ala Pro Ser Gln Ala Ser Gln Ala Ala  
 195 200 205  
 Leu His Val Pro Tyr Ala Thr Ile Asn Thr Ser Cys Arg Pro Ala Thr  
 210 215 220  
 Leu Asp Thr Ala His Pro His Gly Gly Pro Ser Trp Trp Ala Ser Leu  
 225 230 235 240  
 Pro Thr His Ala Ala His Arg Pro Gln Gly Pro Ala Ala Trp Ala Ser  
 245 250 255  
 Thr Pro Ile Pro Ala Arg Gly Ser Phe Val Ser Val Glu Asn Gly Leu  
 260 265 270  
 Tyr Ala Gln Ala Gly Glu Arg Pro Pro His Thr Gly Pro Gly Leu Thr  
 275 280 285  
 Leu Phe Pro Asp Pro Arg Gly Pro Arg Ala Met Glu Gly Pro Leu Gly  
 290 295 300  
 Val Arg  
 305

<210> 253  
 <211> 191  
 <212> PRT  
 <213> Homo sapiens

<400> 253  
 Met Gly Trp Ser Arg Gly Glu Gly Gln Gln Gly Trp Leu Ala Ala Ala  
 1 5 10 15  
 Leu Cys Gly Trp Thr Arg Leu Gly Lys Ala Glu Gly Ser Glu Gly Trp  
 20 25 30  
 Ala Thr Leu Glu Gly Cys Gln Val Pro Ser Leu Leu Gln Gly Asn Glu  
 35 40 45  
 Gly Gly Ala Ala Leu Asn Arg His Met Pro Lys Gln Gly Ile Asp Ala  
 50 55 60  
 Trp Ile Lys Leu Ala Thr Thr Arg Arg Ser Leu Phe Gly Ile Phe Gln  
 65 70 75 80  
 Ile Leu Arg His Pro Ser Cys Asp Asp Gly Val Glu Arg Gly Thr Gly  
 85 90 95  
 Pro Leu Glu Phe Cys Gly Leu His Arg His Ser Ala Gly Ile Trp Thr  
 100 105 110  
 Cys Arg Leu Val Gly Pro Ala Gly Ser Leu Leu Pro Ala Leu Leu Arg  
 115 120 125  
 Gly Arg Gly Gln Leu Gly Gly Arg Gly Leu Ala Glu Lys Gln Lys Asn  
 130 135 140

140

Met Gly Cys Gly Ala Pro Ser Ala Ala Arg Gly Ser Asn Pro Ser Ser  
 145 150 155 160  
 Ser Met Trp Glu Pro Ser Thr Pro Gly Ser Leu Ser Gln Pro Cys Leu  
 165 170 175  
 Gly Pro Gly Trp Glu Asn Pro Thr Pro Gln Gly Cys Gly Glu Gly  
 180 185 190

<210> 254  
 <211> 146  
 <212> PRT  
 <213> Homo sapiens

<400> 254  
 Met Arg Leu Phe Val Ser Val Thr Val Leu Val Ile Cys Leu Ala Asp  
 1 5 10 15  
 Leu Glu Glu Glu Ser Glu Ser Trp Asp Asn Ser Glu Ser Glu Glu Glu  
 20 25 30  
 Glu Lys Ala Pro Val Leu Pro Glu Ser Thr Glu Gly Arg Glu Leu Thr  
 35 40 45  
 Gln Gly Pro Ala Glu Ser Ser Ser Leu Ser Gly Cys Gly Ser Trp Gln  
 50 55 60  
 Pro Arg Lys Leu Pro Val Phe Lys Ser Leu Arg His Met Arg Gln Val  
 65 70 75 80  
 Gly Gly Arg Gly Thr Ala His Gln Glu Leu Arg Arg Arg Ala Asn His  
 85 90 95  
 Gly Leu Ser Leu Pro Thr Arg Leu Ala Ser Gly Pro Ser Thr Phe Lys  
 100 105 110  
 Thr Leu Gln Glu Val Thr Asp Ser Leu Leu Gly Gly Trp Leu Arg Ala  
 115 120 125  
 Gln Gly Val Gly Gly Ile Ser His Arg Ile Ser Ala Pro Leu Ser Val  
 130 135 140  
 Met Thr  
 145

<210> 255  
 <211> 777  
 <212> PRT  
 <213> Homo sapiens

<400> 255  
 Met Ile Leu Leu Ile Ile Leu Trp Ile Leu Arg Glu Ile Gln Ser Ile  
 1 5 10 15  
 Tyr Ile Ile Gly Ile Phe Arg Asn Pro Phe Tyr Pro Lys Asp Val Gln  
 20 25 30  
 Thr Val Thr Val Phe Phe Glu Lys Gln Thr Arg Leu Met Lys Ile Gly  
 35 40 45  
 Ile Val Arg Arg Ile Leu Leu Thr Leu Val Ser Pro Phe Ala Met Ile  
 50 55 60

141

Ala	Phe	Leu	Ser	Leu	Asp	Ser	Ser	Leu	Gln	Gly	Leu	His	Ser	Val	Ser	
65					70					75					80	
Val	Cys	Ile	Gly	Phe	Thr	Arg	Ala	Phe	Arg	Met	Val	Trp	Gln	Asn	Thr	
				85					90					95		
Glu	Asn	Ala	Leu	Leu	Glu	Thr	Val	Ile	Val	Ser	Thr	Val	His	Leu	Ile	
			100					105					110			
Ser	Ser	Thr	Asp	Ile	Trp	Trp	Asn	Arg	Ser	Leu	Asp	Thr	Gly	Leu	Arg	
		115					120					125				
Leu	Leu	Leu	Val	Gly	Ile	Ile	Arg	Asp	Arg	Leu	Ile	Gln	Phe	Ile	Ser	
		130				135					140					
Lys	Leu	Gln	Phe	Ala	Val	Thr	Val	Leu	Leu	Thr	Ser	Trp	Thr	Glu	Lys	
145					150					155					160	
Lys	Gln	Arg	Arg	Lys	Thr	Thr	Ala	Thr	Leu	Cys	Ile	Leu	Asn	Ile	Val	
				165					170					175		
Phe	Ser	Pro	Phe	Val	Leu	Val	Ile	Ile	Val	Phe	Ser	Thr	Leu	Leu	Ser	
			180					185					190			
Ser	Pro	Leu	Leu	Pro	Leu	Phe	Thr	Leu	Pro	Val	Phe	Leu	Val	Gly	Phe	
		195					200					205				
Pro	Arg	Pro	Ile	Gln	Ser	Trp	Pro	Gly	Ala	Ala	Gly	Thr	Thr	Ala	Cys	
		210				215					220					
Val	Cys	Ala	Asp	Thr	Val	Tyr	Tyr	Tyr	Gln	Met	Val	Pro	Arg	Leu	Thr	
225					230					235					240	
Ala	Val	Leu	Gln	Thr	Ala	Met	Ala	Ala	Gly	Ser	Leu	Gly	Leu	Leu	Leu	
				245					250					255		
Pro	Gly	Ser	His	Tyr	Leu	Gly	Arg	Phe	Gln	Asp	Arg	Leu	Met	Trp	Ile	
			260					265					270			
Met	Ile	Leu	Glu	Cys	Gly	Tyr	Thr	Tyr	Cys	Ser	Ile	Asn	Ile	Lys	Gly	
		275					280					285				
Leu	Glu	Leu	Gln	Glu	Thr	Ser	Cys	His	Thr	Ala	Glu	Ala	Arg	Arg	Val	
		290				295					300					
Asp	Glu	Val	Phe	Glu	Asp	Ala	Phe	Glu	Gln	Glu	Tyr	Thr	Arg	Val	Cys	
305					310					315					320	
Ser	Leu	Asn	Glu	His	Phe	Gly	Asn	Val	Leu	Thr	Pro	Cys	Thr	Val	Leu	
				325					330					335		
Pro	Val	Lys	Leu	Tyr	Ser	Asp	Ala	Arg	Asn	Val	Leu	Ser	Gly	Ile	Ile	
			340				345						350			
Asp	Ser	His	Glu	Asn	Leu	Lys	Asp	Phe	Lys	Gly	Asp	Leu	Ile	Lys	Val	
		355					360					365				
Leu	Val	Trp	Ile	Leu	Val	Gln	Tyr	Cys	Ser	Lys	Arg	Pro	Gly	Met	Lys	
		370				375					380					
Glu	Asn	Val	His	Asn	Thr	Glu	Asn	Lys	Gly	Lys	Ala	Pro	Leu	Met	Leu	
385					390					395					400	
Pro	Ala	Leu	Asn	Thr	Leu	Pro	Pro	Pro	Lys	Ser	Pro	Glu	Asp	Ile	Asp	
				405					410					415		

Ser Leu Asn Ser Glu Thr Phe Asn Asp Trp Ser Asp Asp Asn Ile Phe  
 420 425 430  
 Asp Asp Glu Pro Thr Ile Lys Lys Val Ile Glu Glu Lys His Gln Leu  
 435 440 445  
 Lys Asp Leu Pro Gly Thr Asn Leu Phe Ile Pro Gly Ser Val Glu Ser  
 450 455 460  
 Gln Arg Val Gly Asp His Ser Thr Gly Thr Val Pro Glu Asn Asp Leu  
 465 470 475 480  
 Tyr Lys Ala Val Leu Leu Gly Tyr Pro Ala Val Asp Lys Gly Lys Gln  
 485 490 495  
 Glu Asp Met Pro Tyr Ile Pro Leu Met Glu Phe Ser Cys Ser His Ser  
 500 505 510  
 His Leu Val Cys Leu Pro Ala Glu Trp Arg Thr Ser Cys Met Pro Ser  
 515 520 525  
 Ser Lys Met Lys Glu Met Ser Ser Leu Phe Pro Glu Asp Trp Tyr Gln  
 530 535 540  
 Phe Val Leu Arg Gln Leu Glu Cys Tyr His Ser Glu Glu Lys Ala Ser  
 545 550 555 560  
 Asn Val Leu Glu Glu Ile Ala Lys Asp Lys Val Leu Lys Asp Phe Tyr  
 565 570 575  
 Val His Thr Val Met Thr Cys Tyr Phe Ser Leu Phe Gly Ile Asp Asn  
 580 585 590  
 Met Ala Pro Ser Pro Gly His Ile Leu Arg Val Tyr Gly Gly Val Leu  
 595 600 605  
 Pro Trp Ser Val Ala Leu Asp Trp Leu Thr Glu Lys Pro Glu Leu Phe  
 610 615 620  
 Gln Leu Ala Leu Lys Ala Phe Arg Tyr Thr Leu Lys Leu Met Ile Asp  
 625 630 635 640  
 Lys Ala Ser Leu Gly Pro Ile Glu Asp Phe Arg Glu Leu Ile Lys Tyr  
 645 650 655  
 Leu Glu Glu Tyr Glu Arg Asp Trp Tyr Ile Gly Leu Val Ser Asp Glu  
 660 665 670  
 Lys Trp Lys Glu Ala Ile Leu Gln Glu Lys Pro Tyr Leu Phe Ser Leu  
 675 680 685  
 Gly Tyr Asp Ser Asn Met Gly Ile Tyr Thr Gly Arg Val Leu Ser Leu  
 690 695 700  
 Gln Glu Leu Leu Ile Gln Val Gly Lys Leu Asn Pro Glu Ala Val Arg  
 705 710 715 720  
 Gly Gln Trp Ala Asn Leu Ser Trp Glu Leu Leu Tyr Ala Thr Asn Asp  
 725 730 735  
 Asp Glu Glu Arg Tyr Ser Ile Gln Ala His Pro Leu Leu Leu Arg Asn  
 740 745 750  
 Leu Thr Val Gln Ala Ala Glu Pro Pro Leu Gly Tyr Pro Ile Tyr Ser  
 755 760 765

143

Ser Lys Pro Leu His Ile His Leu Tyr  
 770 775

<210> 256  
 <211> 217  
 <212> PRT  
 <213> Homo sapiens

<400> 256  
 Met Glu Met Ala Ser Ser Ala Gly Ser Trp Leu Ser Gly Cys Leu Ile  
 1 5 10 15  
 Pro Leu Val Phe Leu Arg Leu Ser Val His Val Ser Gly His Ala Gly  
 20 25 30  
 Asp Ala Gly Lys Phe His Val Ala Leu Leu Gly Gly Thr Ala Glu Leu  
 35 40 45  
 Leu Cys Pro Leu Ser Leu Trp Pro Gly Thr Val Pro Lys Glu Val Arg  
 50 55 60  
 Trp Leu Arg Ser Pro Phe Pro Gln Arg Ser Gln Ala Val His Ile Phe  
 65 70 75 80  
 Arg Asp Gly Lys Asp Gln Asp Glu Asp Leu Met Pro Glu Tyr Lys Gly  
 85 90 95  
 Arg Thr Val Leu Val Arg Asp Ala Gln Glu Gly Ser Val Thr Leu Gln  
 100 105 110  
 Ile Leu Asp Val Arg Leu Glu Asp Gln Gly Ser Tyr Arg Cys Leu Ile  
 115 120 125  
 Gln Val Gly Asn Leu Ser Lys Glu Asp Thr Val Ile Leu Gln Val Ala  
 130 135 140  
 Ala Pro Ser Val Gly Ser Leu Ser Pro Ser Ala Val Ala Leu Ala Val  
 145 150 155 160  
 Ile Leu Pro Val Leu Val Leu Leu Ile Met Val Cys Leu Cys Leu Ile  
 165 170 175  
 Trp Lys Gln Arg Arg Ala Lys Glu Lys Leu Leu Tyr Glu His Val Thr  
 180 185 190  
 Glu Thr Ile Phe Phe Gln Thr Met Leu Lys Lys Lys Glu Asn Ser Ile  
 195 200 205  
 Lys Leu Ser Arg Asn Ser Gly Val Asn  
 210 215

<210> 257  
 <211> 93  
 <212> PRT  
 <213> Homo sapiens

<400> 257  
 Met Ser His Cys Cys Ser Leu Arg Val Asp Phe Ser Val Pro Leu Cys  
 1 5 10 15  
 Met Leu Leu Ser Pro Leu Leu Gly Met Ser Phe Ser Ala Cys Gln Thr

144

20	25	30
Pro Ser Lys Ser Ser Ser Asp Val Thr Phe Ser Leu Ser Thr Pro Asp		
35	40	45
Pro Thr Pro Gln Ile Asp Leu Val Gln Pro Ser Ser Gly Phe Pro Gln		
50	55	60
His Ser Val Gln Phe Glu Arg Ser Phe Ile Ile Val Ile Ile Thr Phe		
65	70	75
Phe Lys Asn Asn Phe Ile Phe Ile Asn Leu Ile Arg Leu		
85	90	

<210> 258  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<400> 258  
 Met Leu His Ser Leu Ala Leu Ala Glu Phe Cys Arg Asp Trp Gln His  
 1 5 10 15  
 Cys Val Pro Ala Cys Ser Pro Thr Val Ala Val Leu Phe Pro Arg Val  
 20 25 30  
 Gln Arg Arg Phe Phe Leu Cys Ala Leu Trp Leu Leu Arg Ala His Gly  
 35 40 45  
 Gly Gly Leu Gly Ser Ala Ile Gln Asp Cys Leu Phe Tyr Pro Leu His  
 50 55 60  
 Cys Leu Phe Gln Gln Tyr Glu Gly Thr Val Ile Ala His Met Ile Phe  
 65 70 75 80  
 Gly Ser Tyr Glu Gly Ala Phe Cys Val Gly Gly Cys Gln Ile Trp Cys  
 85 90 95  
 Ser Cys Arg Glu Asp Asn Arg Trp Arg Leu Leu Phe Gly His Ile Ala  
 100 105 110  
 Leu Pro Pro Ile Pro Ala Cys Phe Tyr Phe  
 115 120

<210> 259  
 <211> 113  
 <212> PRT  
 <213> Homo sapiens

<400> 259  
 Met Gly Ala Ala Trp Pro Arg Arg Ala Arg Ser Trp Trp Ile Arg Thr  
 1 5 10 15  
 Ser Thr Ala Ser Ser Pro Ser Pro Ser Ser Ile Thr Leu Leu Trp  
 20 25 30  
 Thr Pro Cys Met Trp Ala Glu Ser Trp Ala Cys Cys Ser Ser Pro Thr  
 35 40 45  
 Tyr Thr Arg Thr Gly Lys Cys Ser Thr Asn Arg Thr Pro Arg Trp Pro  
 50 55 60



145

Pro Ala Leu Thr Ser Met Pro Arg Thr Ser Thr Phe Gln Gln Trp Leu  
 65 70 75 80

Ser Ser Pro Thr Phe Trp Trp Leu Val Leu Arg Trp Gly Pro Arg Ile  
 85 90 95

Gly Ser Pro Gln Thr Ser Trp Gly Cys Lys Arg Ala Gln Pro Trp Pro  
 100 105 110

Gly

<210> 260  
 <211> 215  
 <212> PRT  
 <213> Homo sapiens

<400> 260  
 Met Asn Lys Arg Ala Lys Phe Glu Leu Arg Lys Pro Leu Val Leu Trp  
 1 5 10 15

Ser Leu Thr Leu Ala Val Phe Ser Ile Phe Gly Ala Leu Arg Thr Gly  
 20 25 30

Ala Tyr Met Val Tyr Ile Leu Met Thr Lys Gly Leu Lys Gln Ser Val  
 35 40 45

Cys Asp Gln Gly Phe Tyr Asn Gly Pro Val Ser Lys Phe Trp Ala Tyr  
 50 55 60

Ala Phe Val Leu Ser Lys Ala Pro Glu Leu Gly Asp Thr Ile Phe Ile  
 65 70 75 80

Ile Leu Arg Lys Gln Lys Leu Ile Phe Leu His Trp Tyr His His Ile  
 85 90 95

Thr Val Leu Leu Tyr Ser Trp Tyr Ser Tyr Lys Asp Met Val Ala Gly  
 100 105 110

Gly Gly Trp Phe Met Thr Met Asn Tyr Gly Val His Ala Val Met Tyr  
 115 120 125

Ser Tyr Tyr Ala Leu Arg Ala Ala Gly Phe Arg Val Ser Arg Lys Phe  
 130 135 140

Ala Met Phe Ile Thr Leu Ser Gln Ile Thr Gln Met Leu Met Gly Cys  
 145 150 155 160

Val Val Asn Tyr Leu Val Phe Cys Trp Met Gln His Asp Gln Cys His  
 165 170 175

Ser His Phe Gln Asn Ile Phe Trp Ser Ser Leu Met Tyr Leu Ser Tyr  
 180 185 190

Leu Val Leu Phe Cys His Phe Phe Glu Ala Tyr Ile Gly Lys Met  
 195 200 205

Arg Lys Thr Thr Lys Ala Glu  
 210 215

<210> 261  
 <211> 84

146

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 261

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Met Gly Asp Lys Glu Ser Ser Ser Ser Lys Pro Ser Leu Ala Gly Trp
 1          5          10          15
Val Pro Leu Leu Leu Gly Gly Ala Phe Ser Cys Thr Pro Leu Pro Pro
          20          25          30
Arg Gly Glu Ser Gln Gln Pro Asn Gln Thr Ala Gln Val Val His Leu
          35          40          45
Met Glu Thr Thr Gly Leu Lys His Val Leu Tyr Ser Pro Val Tyr Phe
          50          55          60
Cys Cys Tyr Phe Glu Ala Trp Lys Phe Leu Phe Gly Gly Ser Trp Gly
          65          70          75          80
Tyr Ser Ser Gly

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&lt;210&gt; 262

&lt;211&gt; 116

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 262

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Met Ala Leu Asp Ile Ser Leu Phe Tyr Leu Phe Tyr Phe Phe Phe Phe
 1          5          10          15
Leu Arg Trp Asn Phe Ser Leu Ile Ala Gln Ala Gly Val Gln Trp His
          20          25          30
Asp Leu Gly Ser Pro Gln Pro Pro Pro Gly Leu Lys Arg Phe Ser
          35          40          45
Phe Leu Gly Leu Pro Ser Ser Trp Asp Tyr Arg His Ala Pro Pro Cys
          50          55          60
Pro Ala Asn Phe Val Phe Leu Val Glu Met Gly Phe Leu His Val Gly
          65          70          75          80
Gln Ala Gly Leu Glu Leu Pro Thr Ser Gly Gly Pro Pro Ala Trp Ala
          85          90          95
Ser Gln Ser Ala Gly Ile Thr Gly Val Ser His Arg Ala Trp Pro Glu
          100          105          110
Asn Ser His Phe
          115

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&lt;210&gt; 263

&lt;211&gt; 139

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 263

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Met Leu Ala Met Leu Leu Cys Met Leu Val Ser Val Phe Ile Leu Gly
 1          5          10          15
Val Pro Tyr Arg Gly Ser Leu Leu Ile Leu Phe Phe Ile Ser Ser Leu

```

147

20                      25                      30  
 Phe Leu Leu Ser Thr Leu Gly Met Gly Leu Leu Ile Ser Thr Ile Thr  
                     35                      40                      45  
 Arg Asn Gln Phe Asn Ala Ala Gln Val Ala Leu Asn Ala Ala Phe Leu  
                     50                      55                      60  
 Pro Ser Ile Met Leu Ser Gly Phe Ile Phe Gln Ile Asp Ser Met Pro  
                     65                      70                      75                      80  
 Ala Val Ile Arg Ala Val Thr Tyr Ile Ile Pro Ala Arg Tyr Phe Val  
                     85                      90                      95  
 Ser Thr Leu Gln Ser Leu Phe Leu Ala Gly Asn Ile Pro Val Val Leu  
                     100                      105                      110  
 Val Val Asn Val Leu Phe Leu Ile Ala Ser Ala Val Met Phe Ile Gly  
                     115                      120                      125  
 Leu Thr Trp Leu Lys Thr Lys Arg Arg Leu Asp  
                     130                      135

<210> 264  
 <211> 82  
 <212> PRT  
 <213> Homo sapiens

<400> 264  
 Met Gly Trp Gln Leu Arg Ala Leu Ser Ala Val Gly Leu Trp Phe Thr  
                     1                      5                      10                      15  
 Ala Gly Asp Ser His Leu Ser Val Gln Val Cys Gly Gly Gly Pro Ala  
                     20                      25                      30  
 Leu Thr Leu Trp His Leu Arg Ser Ser Thr Pro Thr Thr Ile Phe Pro  
                     35                      40                      45  
 Ile Arg Ala Pro Gln Lys His Val Thr Phe Tyr Gln Asp Leu Val Arg  
                     50                      55                      60  
 Pro Cys Val Ser Leu Leu Pro Pro Pro Leu Thr Leu Pro Phe Ser Pro  
                     65                      70                      75                      80  
 Asp Pro

<210> 265  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<400> 265  
 Met Leu Cys His Ala Trp Leu Leu Leu Met Tyr Leu Phe Leu Glu Met  
                     1                      5                      10                      15  
 Arg Ser His Cys Val Ala Gln Thr Gly Leu Glu Leu Leu Ala Ser Ser  
                     20                      25                      30  
 His Pro Pro Phe Ser Ala Ser Thr Val Ala Gly Ile Ser Gly Thr Cys  
                     35                      40                      45

148

His Cys Ala Leu Leu Ile Pro Phe Lys Ile Arg  
 50 55

<210> 266  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 266  
 Met Ile His Leu Phe Leu Leu Pro Cys Pro Asn Cys Val Phe Leu Leu  
 1 5 10 15  
 Leu His Leu Phe Phe Gln Gln Cys Ala Ala Ser Trp Thr Thr Ser  
 20 25 30

<210> 267  
 <211> 87  
 <212> PRT  
 <213> Homo sapiens

<400> 267  
 Met Thr Leu Leu Leu Thr Leu Glu Val Asp Ser Gly Thr Gln Gln Arg  
 1 5 10 15  
 Ala Gly Val Gly Ser Gln Gly Gln Ala Val Leu Pro Gly Leu Thr Cys  
 20 25 30  
 Phe Leu Leu Thr Phe Leu Leu Ala Ala Ser Val Tyr Ile Thr Gln Ser  
 35 40 45  
 Ala Trp Asp Asn Val Glu Val Ala Glu Val Thr Gly Tyr Phe Met Phe  
 50 55 60  
 Leu His Gly Ile Phe Leu Phe Leu Ile Gly Arg Arg Arg Gln Lys Leu  
 65 70 75 80  
 Glu Glu Met Gly Leu Leu Ser  
 85

<210> 268  
 <211> 73  
 <212> PRT  
 <213> Homo sapiens

<400> 268  
 Met Tyr Pro Val Tyr Thr Thr Ser Asp Phe Cys Ser Gly Thr Phe Val  
 1 5 10 15  
 Leu Ile Phe Ala Trp Leu Thr Leu Ser Glu Leu Val Arg Val Leu His  
 20 25 30  
 Arg Lys Ile Ile Asn Trp Phe Phe Ile Phe Leu Arg Arg Phe Tyr Tyr  
 35 40 45  
 Gly Glu Leu Ala Tyr Ala Asn Met Glu Thr Thr Met Cys His Leu Gln  
 50 55 60  
 Ala Gly Asp Pro Arg Gln Leu Val Val  
 65 70

149

<210> 269  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<400> 269  
 Met Tyr Ser Pro Ser Leu Tyr Leu Leu Pro Ser Leu Pro Ser Leu Leu  
           1                  5                  10                  15  
 Gln Leu Ser Leu Ser Arg Ser Pro Arg Phe Asn Lys Gly Leu Gln Arg  
                   20                  25                  30  
 Ala Met Glu Lys Thr Met Lys Gly Ser Thr Ile Lys Ile Leu Leu Tyr  
           35                  40                  45  
 Phe Phe His His Ile Tyr Ala Ser Leu His Thr Phe Ile Pro Leu Pro  
           50                  55                  60  
 Asn Pro Ser Ile Phe Leu Cys Ile Ser Lys Tyr Ile Ala Asp Ile Ser  
           65                  70                  75                  80  
 Thr

<210> 270  
 <211> 52  
 <212> PRT  
 <213> Homo sapiens

<400> 270  
 Met Ser Lys Lys Ser Val Ser Tyr Lys Ile Arg Tyr Phe Ser Gln Ala  
           1                  5                  10                  15  
 Trp Gln Leu Met Pro Val Ile Leu Val Leu Trp Glu Ala Glu Ala Gly  
                   20                  25                  30  
 Gly Ser Leu Glu Ala Arg Gln Asp His Ile Val Arg Leu Cys Leu Cys  
           35                  40                  45  
 Lys Lys Lys Lys  
           50

<210> 271  
 <211> 83  
 <212> PRT  
 <213> Homo sapiens

<400> 271  
 Met Leu Cys Ser Ser Phe Leu Pro Leu Ser Thr Ala Ala Ile Trp Ala  
           1                  5                  10                  15  
 Ala Leu Phe Ser Gly Met Gly Ala Val Arg His Ser Pro Ser Glu Gly  
                   20                  25                  30  
 Lys Arg Ser Leu Lys Ser Ser Arg Cys Leu His Phe Trp Pro Leu Pro  
           35                  40                  45  
 Thr Gly Cys Ser Ser Pro Pro Pro Cys Asn Val Thr Thr Lys Asn  
           50                  55                  60

150

Val Ser Arg Cys Cys Gln Lys Ser Ser Arg Asp Gly Arg Val Arg Leu  
 65 70 75 80

Pro Pro Arg

<210> 272  
 <211> 84  
 <212> PRT  
 <213> Homo sapiens

<400> 272  
 Met Gly Leu Arg Leu Pro Pro Pro Leu Cys Trp Phe Leu Cys Leu Thr  
 1 5 10 15  
 Ser Thr Gly Gln Val Pro Met Ala Gln Ala Arg Ala Gly Val Gln Gly  
 20 25 30  
 Pro Met Asp Gly Arg Met Pro Ser Asn Gly Cys Leu Pro Val Ser Pro  
 35 40 45  
 Arg Thr Pro Tyr Gly Met Pro Tyr Leu Gly Ala Leu Trp Pro Cys Trp  
 50 55 60  
 Pro Cys Ser Trp Gln Gly Arg Ser Thr Ser Arg His Pro Cys Gln Gln  
 65 70 75 80  
 Asp Leu Ser Gly

<210> 273  
 <211> 230  
 <212> PRT  
 <213> Homo sapiens

<400> 273  
 Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu  
 1 5 10 15  
 Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys  
 20 25 30  
 Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp  
 35 40 45  
 Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala  
 50 55 60  
 Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu  
 65 70 75 80  
 Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Glu Pro Gly Glu Glu  
 85 90 95  
 Gly Arg Tyr Lys Gln Lys Phe Gln Ser Val Phe Thr Val Thr Arg Gln  
 100 105 110  
 Thr His Gln Pro Pro Ala Pro Asn Ser Leu Ile Arg Phe Asn Ala Val  
 115 120 125  
 Leu Thr Asn Pro Gln Gly Asp Tyr Asp Thr Ser Thr Gly Lys Phe Thr  
 130 135 140

151

Cys Lys Val Pro Gly Leu Tyr Tyr Phe Val Tyr His Ala Ser His Thr  
 145 150 155 160  
 Ala Asn Leu Cys Val Leu Leu Tyr Arg Ser Gly Val Lys Val Val Thr  
 165 170 175  
 Phe Cys Gly His Thr Ser Lys Thr Asn Gln Val Asn Ser Gly Gly Val  
 180 185 190  
 Leu Leu Arg Leu Gln Val Gly Glu Glu Val Trp Leu Ala Val Asn Asp  
 195 200 205  
 Tyr Tyr Asp Met Val Gly Ile Gln Gly Ser Asp Ser Val Phe Ser Gly  
 210 215 220  
 Phe Leu Leu Phe Pro Asp  
 225 230

<210> 274  
 <211> 83  
 <212> PRT  
 <213> Homo sapiens

<400> 274  
 Met Cys Ala Met Ala Pro Leu Trp Ser Pro Leu Cys Pro Ser Ile Cys  
 1 5 10 15  
 Met Cys Ser Val Ser Leu Ala Cys Val Arg Val Arg Val Ser Ala Tyr  
 20 25 30  
 Ala Ser Thr His Trp Ala Leu Gly Cys Ser Gln Gly Lys Phe Asp Leu  
 35 40 45  
 Glu Arg Leu Ser Ser Pro Trp Asn Gln Asp Phe Leu Ser Pro Pro His  
 50 55 60  
 Pro Gly Pro Val Pro Pro Trp Leu Ser Gly Tyr Trp Gly Met Glu Thr  
 65 70 75 80  
 Leu Gly Glu

<210> 275  
 <211> 91  
 <212> PRT  
 <213> Homo sapiens

<400> 275  
 Met Arg Pro Gln Glu Leu Pro Arg Leu Ala Phe Pro Leu Leu Leu Leu  
 1 5 10 15  
 Leu Leu Leu Leu Leu Pro Pro Pro Pro Cys Pro Ala His Ser Ala Thr  
 20 25 30  
 Arg Phe Asp Pro Thr Trp Glu Ser Leu Asp Ala Arg Gln Leu Pro Ala  
 35 40 45  
 Trp Phe Asp Gln Ala Lys Phe Gly Ile Phe Ile His Trp Gly Val Phe  
 50 55 60  
 Ser Val Pro Ser Phe Gly Ser Glu Trp Phe Trp Leu Tyr Leu Val Gly

152

65		70		75		80				
Val	Arg	Ile	Phe	Val	Glu	Leu	Glu	Cys	His	Arg
				85					90	

<210> 276  
 <211> 336  
 <212> PRT  
 <213> Homo sapiens

<400> 276  
 Met Leu Glu Thr Gly Leu Phe Phe Leu Leu Ser Trp Ser Ala Phe Leu  
   1                  5                  10                  15  
 Ser Ala Glu Ala Ala Gly Leu Thr Gly Ile Val Ala Val Leu Phe Cys  
           20                  25                  30  
 Gly Val Thr Gln Ala His Tyr Thr Tyr Asn Asn Leu Ser Ser Asp Ser  
           35                  40                  45  
 Lys Ile Arg Thr Lys Gln Leu Phe Glu Phe Met Asn Phe Leu Ala Glu  
   50                  55                  60  
 Asn Val Ile Phe Cys Tyr Met Gly Leu Ala Leu Phe Thr Phe Gln Asn  
   65                  70                  75                  80  
 His Ile Phe Asn Ala Leu Phe Ile Leu Gly Ala Phe Leu Ala Ile Phe  
           85                  90                  95  
 Val Ala Arg Ala Cys Asn Ile Tyr Pro Leu Ser Phe Leu Leu Asn Leu  
           100                  105                  110  
 Gly Arg Lys Gln Lys Ile Pro Trp Asn Phe Gln His Met Met Met Phe  
           115                  120                  125  
 Ser Gly Leu Arg Gly Ala Ile Ala Phe Ala Leu Ala Ile Arg Asn Thr  
   130                  135                  140  
 Glu Ser Gln Pro Lys Gln Met Met Phe Thr Thr Thr Leu Leu Leu Val  
  145                  150                  155                  160  
 Phe Phe Thr Val Trp Val Phe Gly Gly Gly Thr Thr Pro Met Leu Thr  
           165                  170                  175  
 Trp Leu Gln Ile Arg Val Gly Val Asp Leu Asp Glu Asn Leu Lys Glu  
           180                  185                  190  
 Asp Pro Ser Ser Gln His Gln Glu Ala Asn Asn Leu Asp Lys Asn Met  
   195                  200                  205  
 Thr Lys Ala Glu Ser Ala Arg Leu Phe Arg Met Trp Tyr Ser Phe Asp  
   210                  215                  220  
 His Lys Tyr Leu Lys Pro Ile Leu Thr His Ser Gly Pro Pro Leu Thr  
  225                  230                  235                  240  
 Thr Thr Leu Pro Glu Trp Cys Gly Pro Ile Ser Arg Leu Leu Thr Ser  
           245                  250                  255  
 Pro Gln Ala Tyr Gly Glu Gln Leu Lys Glu Asp Asp Val Glu Cys Ile  
           260                  265                  270  
 Val Asn Gln Asp Glu Leu Ala Ile Asn Tyr Gln Glu Gln Ala Ser Ser  
   275                  280                  285



153

Pro Cys Ser Pro Pro Ala Arg Leu Gly Leu Asp Gln Lys Ala Ser Pro  
 290 295 300  
 Gln Thr Pro Gly Lys Glu Asn Ile Tyr Glu Gly Asp Leu Gly Leu Gly  
 305 310 315 320  
 Gly Tyr Glu Leu Lys Leu Glu Gln Thr Leu Gly Gln Ser Gln Leu Asn  
 325 330 335

<210> 277  
 <211> 106  
 <212> PRT  
 <213> Homo sapiens

<400> 277  
 Met Gln Trp Leu Leu Ile Thr Pro Arg Leu Phe Tyr Phe Pro Leu Leu  
 1 5 10 15  
 Leu Leu Trp Leu Val Ser Val Lys Phe Leu Phe Ile Phe Ile Phe Gly  
 20 25 30  
 Asp Gly Gln Gly Leu Ala Pro Ser Leu Arg Pro Glu Cys Ser Gly Ala  
 35 40 45  
 Ile Met Ala His His Ser Leu Asp Phe Gln Gly Leu Ser Tyr Pro Pro  
 50 55 60  
 Thr Leu Ala Ser Ala Gly Ala Gly Thr Thr Gly Met His His His Ala  
 65 70 75 80  
 Gln Leu Ile Phe Lys Phe Phe Tyr Arg Asp Gly Val Ser Leu Cys Gly  
 85 90 95  
 Leu Gly Trp Ser Gln Thr Pro Gly His Lys  
 100 105

<210> 278  
 <211> 131  
 <212> PRT  
 <213> Homo sapiens

<400> 278  
 Met Gly Ala Ser Leu Cys Leu Thr Gln Leu Leu Leu Leu Gly Lys  
 1 5 10 15  
 Gly Gly Leu Gly Gln Ala Ser Ile Pro Leu Val Lys Thr Pro Ala Gly  
 20 25 30  
 His Gln Ala Phe Trp Thr Arg Thr His Thr His Thr His Thr His Thr  
 35 40 45  
 His Thr Lys Leu His Ser Arg Pro Ala Ala Val Thr Cys His Gln Glu  
 50 55 60  
 Ser Pro Gln Leu Arg Pro Pro Pro Ile Leu Ser Tyr Glu Lys Pro Leu  
 65 70 75 80  
 Leu Trp Gly Arg Arg Leu Glu Lys Val Gly Cys Gly Gly Gln Glu Gly

154

	85		90		95
Pro Cys Arg	Ala Gly Gly Trp Val	Trp Leu Ser Arg Cys	Phe Pro Glu		
	100	105	110		
Gly Ser Ala	Gly Ile Arg Gly Ser Cys	Gly Arg Glu Arg	Ala Pro Ala		
	115	120	125		
Ser Trp Leu					
	130				

<210> 279  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<400> 279  
 Met Cys Val His Thr Cys Val Cys Met Cys Val His Thr Cys Val Cys  
 1 5 10 15  
 Val His Ala Cys Val Trp Ala His Val Cys Met Cys Val Cys Glu Cys  
 20 25 30  
 Val Cys Trp Gly Gly Gly Met Ala Leu Gly Lys Val Cys Pro Gly Trp  
 35 40 45  
 Lys Pro His Ser Leu Pro Ser Ala Trp Arg Trp Ala Cys Ala Trp Arg  
 50 55 60  
 Pro Ile Ala Arg Arg Leu Arg Pro Thr Gly Ala Thr Ser Thr Val Pro  
 65 70 75 80  
 Leu

<210> 280  
 <211> 108  
 <212> PRT  
 <213> Homo sapiens

<400> 280  
 Met His Pro Pro Pro Gly Val Trp Leu Leu His Leu His Thr Pro Leu  
 1 5 10 15  
 Arg Gly Phe Cys Leu Pro Leu Pro Leu Arg Ser Gln Glu Ala Val Pro  
 20 25 30  
 Gly Arg Gly Arg Arg His Leu Ser Pro Gln Leu Leu Thr Pro His Pro  
 35 40 45  
 Leu Thr Ser Ser Pro Phe Val Lys Tyr Thr Gln Asp Glu Thr Cys Thr  
 50 55 60  
 Gln Trp Leu Thr Ala Ala Arg Phe Val Thr Ala Arg Gly Gly Glu His  
 65 70 75 80  
 Arg Thr Pro Ser Glu Gly Glu Gly Ile Ser Thr Ala Pro Pro Pro Cys  
 85 90 95  
 Trp Asn Glu Thr Gln Pro Gln Gly Gly Ala Lys Leu  
 100 105

155

<210> 281  
 <211> 49  
 <212> PRT  
 <213> Homo sapiens

<400> 281  
 Met Ser Cys Thr Leu Leu Ile Cys Thr Val Val Leu Gly Val Thr Thr  
     1                    5                    10                    15  
 Pro Ala Ile Gly Pro Ala Ala Pro Ser Leu Leu Ala Thr Pro Pro Gln  
                     20                    25                    30  
 Ala Ala Ala Ala Thr Met Gln Pro Arg Leu Gly Arg Ala Ala Gly Ala  
                     35                    40                    45  
 Ala

<210> 282  
 <211> 187  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 282  
 Xaa Ala Arg Asp Leu Leu Gln Ala Leu Arg His Pro Lys Ala Val Ala  
     1                    5                    10                    15  
 Phe Gly Glu Met Gly Leu Asp Tyr Ser Tyr Lys Cys Thr Thr Pro Val  
                     20                    25                    30  
 Pro Glu Gln His Lys Val Phe Glu Arg Gln Leu Gln Leu Ala Val Ser  
                     35                    40                    45  
 Leu Lys Lys Pro Leu Val Ile His Cys Arg Glu Ala Asp Glu Asp Leu  
     50                    55                    60  
 Leu Glu Ile Met Lys Lys Phe Val Pro Pro Asp Tyr Lys Ile His Arg  
     65                    70                    75                    80  
 His Cys Phe Thr Gly Ser Tyr Pro Val Ile Glu Pro Leu Leu Lys Tyr  
                     85                    90                    95  
 Phe Pro Asn Met Ser Val Gly Phe Thr Ala Val Leu Thr Tyr Ser Ser  
                     100                    105                    110  
 Ala Trp Glu Ala Arg Glu Ala Leu Arg Gln Ile Pro Leu Glu Arg Ile  
     115                    120                    125  
 Ile Val Glu Thr Asp Ala Pro Tyr Phe Leu Pro Arg Gln Val Pro Lys  
     130                    135                    140  
 Ser Leu Cys Gln Tyr Ala His Pro Gly Leu Ala Leu His Thr Val Arg  
     145                    150                    155                    160  
 Glu Ile Ala Arg Val Lys Asp Gln Pro Leu Ser Leu Thr Leu Ala Ala  
                     165                    170                    175

156

Leu Arg Glu Asn Thr Ser Arg Leu Tyr Ser Leu  
 180 185

&lt;210&gt; 283

&lt;211&gt; 95

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (80)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 283

Met Val Pro Cys Arg Lys Thr Leu Leu Phe Leu Trp Val Gly Ser Leu  
 1 5 10 15

Cys Arg Asp Val Gly Ser Trp Ser Gly Trp Pro Phe Gly Leu Ser Thr  
 20 25 30

Ala Thr Gln Pro Arg Leu Arg Leu Gly Lys Gln Thr Gly Ala Gly Gln  
 35 40 45

Ala Arg Arg Ala Cys Arg Thr Val Ile Leu Arg Cys Gly Ser Cys Cys  
 50 55 60

Arg Gly Arg Arg Thr Gly Ser Val Val Ala Trp Ser Ser Leu Pro Xaa  
 65 70 75 80

Arg Thr Ser Ala Ala Glu Leu Arg Trp Arg Pro Trp Gly Pro Val  
 85 90 95

&lt;210&gt; 284

&lt;211&gt; 175

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 284

Met Ala Thr Pro Xaa Gly Leu Gly Ala Leu Leu Leu Leu Leu Leu  
 1 5 10 15

Pro Thr Ser Gly Gln Glu Lys Pro Thr Glu Gly Pro Arg Asn Thr Cys  
 20 25 30

Leu Gly Ser Asn Asn Met Tyr Asp Ile Phe Asn Leu Asn Asp Lys Ala  
 35 40 45

Leu Cys Phe Thr Lys Cys Arg Gln Ser Gly Ser Asp Ser Cys Asn Val  
 50 55 60

Glu Asn Leu Gln Arg Tyr Trp Leu Asn Tyr Glu Ala His Leu Met Lys  
 65 70 75 80

Glu Gly Leu Thr Gln Lys Val Asn Thr Pro Phe Leu Lys Ala Leu Val  
 85 90 95

Gln Asn Leu Ser Thr Asn Thr Ala Glu Asp Phe Tyr Phe Ser Leu Glu

157

100	105	110
Pro Ser Gln Val Pro Arg Gln Val Met Lys Asp Glu Asp Lys Pro Pro		
115	120	125
Asp Arg Val Arg Leu Pro Lys Ser Leu Phe Arg Ser Leu Pro Gly Asn		
130	135	140
Arg Ser Val Val Arg Leu Ala Val Thr Ile Leu Asp Ile Gly Pro Gly		
145	150	155
Thr Leu Phe Lys Val Arg Thr Gln Gly Ser Ser Lys Val Lys Cys		
165	170	175

&lt;210&gt; 285

&lt;211&gt; 126

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (99)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 285

Met Ala Ala Phe Ala Thr Ala His Leu Leu Tyr Val Trp Ala Phe Gly		
1	5	10
Phe Ser Pro Leu Gln Pro Gly Leu Leu Leu Leu Ile Ile Leu Ala Pro		
20	25	30
Gly Pro Tyr Leu Ser Leu Val Leu Gln His Leu Glu Pro Asp Met Val		
35	40	45
Leu Pro Val Ala Ala Tyr Gly Leu Ile Leu Met Ala Met Leu Trp Arg		
50	55	60
Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu Phe Thr		
65	70	75
Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro Leu Pro		
85	90	95
His Ala Xaa Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln Leu Leu		
100	105	110
Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp		
115	120	125

&lt;210&gt; 286

&lt;211&gt; 187

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 286

Met Trp Cys Ala Ser Pro Val Ala Val Val Ala Phe Cys Ala Gly Leu		
1	5	10
Leu Val Ser His Pro Val Leu Thr Gln Gly Gln Glu Ala Gly Gly Arg		
20	25	30
Pro Gly Ala Asp Cys Glu Val Cys Lys Glu Phe Leu Asn Arg Phe Tyr		

158

35					40					45					
Lys	Ser	Leu	Ile	Asp	Arg	Gly	Val	Asn	Phe	Ser	Leu	Asp	Thr	Ile	Glu
50						55					60				
Lys	Glu	Leu	Ile	Ser	Phe	Cys	Leu	Asp	Thr	Lys	Gly	Lys	Glu	Asn	Arg
65					70					75				80	
Leu	Cys	Tyr	Tyr	Leu	Gly	Ala	Thr	Lys	Asp	Ala	Ala	Thr	Lys	Ile	Leu
				85					90					95	
Ser	Glu	Val	Thr	Arg	Pro	Met	Ser	Val	His	Met	Pro	Ala	Met	Lys	Ile
			100					105					110		
Cys	Glu	Lys	Leu	Lys	Lys	Leu	Asp	Ser	Gln	Ile	Cys	Glu	Leu	Lys	Tyr
		115					120					125			
Glu	Lys	Thr	Leu	Asp	Leu	Ala	Ser	Val	Asp	Leu	Arg	Lys	Met	Arg	Val
		130				135					140				
Ala	Glu	Leu	Lys	Gln	Ile	Leu	His	Ser	Trp	Gly	Glu	Glu	Cys	Arg	Ala
145					150					155					160
Cys	Ala	Glu	Lys	Thr	Asp	Tyr	Val	Asn	Leu	Ile	Gln	Glu	Leu	Ala	Pro
				165					170					175	
Lys	Tyr	Ala	Ala	Thr	His	Pro	Lys	Thr	Glu	Leu					
				180				185							

&lt;210&gt; 287

&lt;211&gt; 214

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (186)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (188)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (189)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (200)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (202)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (203)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

159

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (204)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (206)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (211)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 287

Met	Ser	Arg	Gly	Leu	Leu	Ala	Val	Arg	Gly	Ala	Phe	Val	Gly	Ala	Ser
1				5					10					15	

Leu	Leu	Phe	Leu	Leu	Val	Asn	Val	Leu	Cys	Ala	Val	Leu	Ser	His	Arg
			20					25					30		

Arg	Arg	Ala	Gln	Pro	Trp	Ala	Leu	Leu	Val	Arg	Val	Leu	Val	Ser	
		35					40				45				

Asp	Ser	Leu	Phe	Val	Ile	Cys	Ala	Leu	Ser	Leu	Ala	Ala	Cys	Leu	Cys
	50					55					60				

Leu	Val	Ala	Arg	Arg	Ala	Pro	Ser	Thr	Ser	Ile	Tyr	Leu	Glu	Ala	Lys
65					70					75					80

Gly	Thr	Ser	Val	Cys	Gln	Ala	Ala	Ala	Met	Gly	Gly	Ala	Met	Val	Leu
			85						90					95	

Leu	Tyr	Ala	Ser	Arg	Ala	Cys	Tyr	Asn	Leu	Thr	Ala	Leu	Ala	Leu	Ala
			100					105				110			

Pro	Gln	Ser	Arg	Leu	Asp	Thr	Phe	Asp	Tyr	Asp	Trp	Tyr	Asn	Val	Ser
		115					120					125			

Asp	Gln	Ala	Asp	Leu	Val	Asn	Asp	Leu	Gly	Asn	Lys	Gly	Tyr	Leu	Val
	130					135					140				

Phe	Gly	Leu	Ile	Leu	Phe	Val	Trp	Glu	Leu	Leu	Pro	Thr	Thr	Leu	Leu
145					150				155						160

Val	Gly	Phe	Phe	Arg	Val	His	Arg	Pro	Pro	Gln	Asp	Leu	Ser	Thr	Ser
				165					170					175	

His	Ile	Pro	Gln	Trp	Ala	Arg	Ser	Phe	Xaa	Ser	Xaa	Xaa	Leu	Leu	Leu
			180					185					190		

Leu	Thr	Gly	Ala	Trp	Ala	Leu	Xaa	Lys	Xaa	Xaa	Xaa	Ala	Xaa	Phe	Leu
		195					200					205			

Gly	Thr	Xaa	Thr	Arg	Val
					210

&lt;210&gt; 288

&lt;211&gt; 254

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

160

<221> SITE  
 <222> (144)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (212)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (214)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (245)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (248)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 288  
 Phe Leu Leu Val Asn Val Leu Cys Ala Val Leu Ser His Arg Arg Arg  
   1                  5                  10                  15  
 Ala Gln Pro Trp Ala Leu Leu Leu Val Arg Val Leu Val Ser Asp Ser  
           20                  25                  30  
 Leu Phe Val Ile Cys Ala Leu Ser Leu Ala Ala Cys Leu Cys Leu Val  
       35                  40                  45  
 Ala Arg Arg Ala Pro Ser Thr Ser Ile Tyr Leu Glu Ala Lys Gly Thr  
       50                  55                  60  
 Ser Val Cys Gln Ala Ala Ala Met Gly Gly Ala Met Val Leu Leu Tyr  
       65                  70                  75                  80  
 Ala Ser Arg Ala Cys Tyr Asn Leu Thr Ala Leu Ala Leu Ala Pro Gln  
           85                  90                  95  
 Ser Arg Leu Asp Thr Phe Asp Tyr Asp Trp Tyr Asn Val Ser Asp Gln  
          100                 105                 110  
 Ala Asp Leu Val Asn Asp Leu Gly Asn Lys Gly Tyr Leu Val Phe Gly  
       115                 120                 125  
 Leu Ile Leu Phe Val Trp Glu Leu Leu Pro Thr Thr Leu Leu Val Xaa  
       130                 135                 140  
 Phe Phe Arg Val His Arg Pro Pro Gln Asp Leu Ser Thr Ser His Ile  
   145                 150                 155                 160  
 Leu Asn Gly Gln Val Phe Ala Ser Arg Ser Tyr Phe Phe Asp Arg Ala  
          165                 170                 175  
 Gly His Cys Glu Asp Glu Gly Cys Ser Trp Glu His Ser Arg Gly Glu  
          180                 185                 190  
 Ser Thr Ser Met Ser Gly Ser Leu Gly Ser Gly Ser Trp Tyr Gly Ala  
       195                 200                 205  
 Ile Gly Arg Xaa Pro Xaa Trp Tyr Gly Gly Ser Gln Thr Lys Thr Thr  
      210                 215                 220



161

Pro Leu Ser Leu Gln Cys Arg Gln Arg Thr His Ser Leu Ser Pro Asn  
 225 230 235 240

Gly Pro Leu Gln Xaa Pro Ala Xaa Leu Leu Ala Gly Ser Val  
 245 250

<210> 289

<211> 221

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (210)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (215)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (217)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 289

Met Gly Gly Met Ile Ile Val Leu Leu Ile Cys Ile Val Trp Phe Pro  
 1 5 10 15

Leu Leu Phe Met Ser Leu Ile Lys Ser Val Ala Gly Val Ile Asn Gln  
 20 25 30

Pro Leu Asp Val Ser Val Thr Ile Thr Leu Gly Gly Tyr Gln Pro Ile  
 35 40 45

Phe Thr Met Ser Ala Gln Gln Ser Gln Leu Lys Ile Met Asp Gln Gln  
 50 55 60

Ser Phe Asn Lys Phe Ile Gln Ala Phe Ser Arg Asp Thr Gly Ala Met  
 65 70 75 80

Gln Phe Leu Glu Asn Tyr Glu Lys Glu Asp Ile Thr Val Ala Glu Leu  
 85 90 95

Glu Gly Asn Ser Asn Ser Leu Trp Thr Ile Ser Pro Pro Ser Lys Gln  
 100 105 110

Lys Met Ile His Glu Leu Leu Asp Pro Asn Ser Ser Phe Ser Val Val  
 115 120 125

Phe Ser Trp Ser Ile Gln Arg Asn Leu Ser Leu Gly Ala Lys Ser Glu  
 130 135 140

Ile Ala Thr Asp Lys Leu Ser Phe Pro Leu Lys Asn Ile Thr Arg Lys  
 145 150 155 160

Asn Ile Ala Lys Met Ile Ala Gly Asn Ser Thr Glu Ser Ser Lys Thr  
 165 170 175

Pro Val Thr Ile Glu Lys Ile Tyr Pro Tyr Tyr Val Lys Ala Pro Ser  
 180 185 190

162

Asp Ser Asn Ser Lys Pro Ile Lys Gln Leu Leu Ser Glu Asn Asn Ser  
 195 200 205

Trp Xaa Leu Pro Ser Phe Xaa Gln Xaa His Thr Leu Asn  
 210 215 220

<210> 290  
 <211> 135  
 <212> PRT  
 <213> Homo sapiens

<400> 290  
 Met Ala Phe Lys Leu Leu Ile Leu Leu Ile Gly Thr Trp Ala Leu Phe  
 1 5 10 15

Phe Arg Lys Arg Arg Ala Asp Met Pro Arg Val Phe Val Phe Arg Ala  
 20 25 30

Leu Leu Leu Val Leu Ile Phe Leu Phe Val Val Ser Tyr Trp Leu Phe  
 35 40 45

Tyr Gly Val Arg Ile Leu Asp Ser Arg Asp Arg Asn Tyr Gln Gly Ile  
 50 55 60

Val Gln Tyr Ala Val Ser Leu Val Asp Ala Leu Leu Phe Ile His Tyr  
 65 70 75 80

Leu Ala Ile Val Leu Leu Glu Leu Arg Gln Leu Gln Pro Met Phe Thr  
 85 90 95

Leu Gln Val Val Pro Leu His Arg Trp Arg Val Pro Leu Leu Gln Pro  
 100 105 110

Gly Thr Pro Glu Tyr Pro Ala Ser Ser Ile Gly Gly Pro Arg Lys Leu  
 115 120 125

Leu Gln Arg Phe His His Leu  
 130 135

<210> 291  
 <211> 295  
 <212> PRT  
 <213> Homo sapiens

<400> 291  
 Met Leu Cys Cys Trp Phe Pro Trp Arg Ile Leu Ala Ala Gly Gln Val  
 1 5 10 15

Pro Tyr Ser Pro His Ser Pro Gln Val Ala Gly Cys Asp Leu Thr Arg  
 20 25 30

Cys Glu Ser Gly Gly Ala Arg Ala Leu Ser Ile Gln Arg Ala Ala Leu  
 35 40 45

Val Val Leu Glu Asn Tyr Tyr Lys Asp Phe Thr Ile Tyr Asn Pro Asn  
 50 55 60

Leu Leu Thr Ala Ser Lys Phe Arg Ala Ala Lys His Met Ala Gly Leu  
 65 70 75 80

Lys Val Tyr Asn Val Asp Gly Pro Ser Asn Asn Ala Thr Gly Gln Ser  
 85 90 95

163

Arg Ala Met Ile Ala Ala Ala Ala Arg Arg Arg Asp Ser Ser His Asn  
                   100                                  105                                  110  
 Glu Leu Tyr Tyr Glu Glu Ala Glu His Glu Arg Arg Val Lys Lys Arg  
                   115                                  120                                  125  
 Lys Ala Arg Leu Val Val Ala Val Glu Glu Ala Phe Ile His Ile Gln  
                   130                                  135                                  140  
 Arg Leu Gln Ala Glu Glu Gln Gln Lys Ala Pro Gly Glu Val Met Asp  
                   145                                  150                                  155                                  160  
 Pro Arg Glu Ala Ala Gln Ala Ile Phe Pro Ser Met Ala Arg Ala Leu  
                                   165                                  170                                  175  
 Gln Lys Tyr Leu Arg Ile Thr Arg Gln Gln Asn Tyr His Ser Met Glu  
                   180                                  185                                  190  
  
 Ser Ile Leu Gln His Leu Ala Phe Cys Ile Thr Asn Gly Met Thr Pro  
                   195                                  200                                  205  
 Lys Ala Phe Leu Glu Arg Tyr Leu Ser Ala Gly Pro Thr Leu Gln Tyr  
                   210                                  215                                  220  
 Asp Lys Asp Arg Trp Leu Ser Thr Gln Trp Arg Leu Val Ser Asp Glu  
                   225                                  230                                  235                                  240  
 Ala Val Thr Asn Gly Leu Arg Asp Gly Ile Val Phe Val Leu Lys Cys  
                                   245                                  250                                  255  
 Leu Asp Phe Ser Leu Val Val Asn Val Lys Lys Ile Pro Phe Ile Ile  
                                   260                                  265                                  270  
 Leu Ser Glu Glu Phe Ile Asp Pro Lys Ser His Lys Phe Val Leu Arg  
                   275                                  280                                  285  
 Leu Gln Ser Glu Thr Ser Val  
                   290                                  295

<210> 292  
 <211> 85  
 <212> PRT  
 <213> Homo sapiens

<400> 292  
 Met Asp Thr Tyr Phe Ile Leu Trp Ala Ile Pro Val Thr Ile Ile Ile  
   1                                  5                                  10                                  15  
 Cys Phe Ser Trp Leu Glu Tyr Ser Gln Thr Trp Ala Leu Gly Ala Ser  
                   20                                  25                                  30  
 Cys Ser Leu Pro Gln Cys Pro Phe Asp Val Met Leu Ser Leu Phe Leu  
                   35                                  40                                  45  
 Val His Pro Tyr Phe Pro Thr Val Trp Asp His Leu Cys Phe Pro His  
                   50                                  55                                  60  
 Pro Ser Pro Glu Ser Ser Pro Phe Ser Lys Cys Ser Leu Val Ala Trp  
                   65                                  70                                  75                                  80  
 Leu Glu Asn Gly Ala  
                                   85

<210> 293  
 <211> 196  
 <212> PRT  
 <213> Homo sapiens

<400> 293  
 Thr Gln Arg Met Ser Gly Lys His Tyr Lys Gly Pro Glu Val Ser Cys  
     1                    5                    10                    15  
 Cys Ile Lys Tyr Phe Ile Phe Gly Phe Asn Val Ile Phe Trp Phe Leu  
                     20                    25                    30  
 Gly Ile Thr Phe Leu Gly Ile Gly Leu Trp Ala Trp Asn Glu Lys Gly  
                     35                    40                    45  
 Val Leu Ser Asn Ile Ser Ser Ile Thr Asp Leu Gly Gly Phe Asp Pro  
                     50                    55                    60  
 Val Trp Leu Phe Leu Val Val Gly Gly Val Met Phe Ile Leu Gly Phe  
                     65                    70                    75                    80  
 Ala Gly Cys Ile Gly Ala Leu Arg Glu Asn Thr Phe Leu Leu Lys Phe  
                     85                    90                    95  
 Phe Ser Val Phe Leu Gly Ile Ile Phe Phe Leu Glu Leu Thr Ala Gly  
                     100                    105                    110  
 Val Leu Ala Phe Val Phe Lys Asp Trp Ile Lys Asp Gln Leu Tyr Phe  
                     115                    120                    125  
 Phe Ile Asn Asn Asn Ile Arg Ala Tyr Arg Asp Asp Ile Asp Leu Gln  
                     130                    135                    140  
 Asn Leu Ile Asp Phe Thr Gln Glu Tyr Ile Pro Met Gln Val Glu Ser  
                     145                    150                    155                    160  
 Asp Val Ala Phe His Ser Pro Ala Ala Leu Lys Ile Pro Gln Lys Met  
                     165                    170                    175  
 Ser Ser Thr Leu Ser Val Ala Met Met Pro Gly Lys Asn Gln Lys Leu  
                     180                    185                    190  
 Thr Ser Arg Leu  
                     195

<210> 294  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (8)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (16)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <400> 294

165

Val Ser Leu Lys Leu Val Ile Xaa Leu Ser Trp Asn Leu Ile Thr Xaa  
 1 5 10 15  
 Val Trp Phe His Lys Asn Leu Thr Phe Gly Ser Trp Leu Ile His Trp  
 20 25 30  
 Glu Gly Pro Ser Gly Phe Phe Asn Phe Gly Gly Ser Gly Leu Gly Lys  
 35 40 45  
 Phe Phe His Leu Lys Leu Asn Leu Met Gly  
 50 55

<210> 295  
 <211> 133  
 <212> PRT  
 <213> Homo sapiens

<400> 295  
 Met His Gly Ala Arg Leu Phe Val Cys Leu Phe Val Cys Phe Arg Gln  
 1 5 10 15  
 Ser Cys Tyr Val Ala Gln Ala Gly Val Gln Trp His Asn His Ser Ser  
 20 25 30  
 Leu Gln Pro Leu Ser Pro Gly Phe Lys Arg Phe Phe Cys Leu Asn Leu  
 35 40 45  
 Pro Ser Ser Trp Asp Tyr Arg His Met Ala Thr Cys Pro Trp Leu Ile  
 50 55 60  
 Phe Val Phe Leu Val Glu Met Glu Phe Arg His Val Gly Gln Ala Gly  
 65 70 75 80  
 Leu Gly Leu Leu Thr Ser Ser Asp Leu Pro Ala Leu Ala Phe Gln Ser  
 85 90 95  
 Ala Gly Ile Thr Gly Leu Ser His His Ala Trp Pro Gly Arg Phe Leu  
 100 105 110  
 Lys Lys Val Ile Glu Ile Cys Ser Cys Pro Val Pro Arg Gly Ser His  
 115 120 125  
 Ala Gly Leu Phe Ser  
 130

<210> 296  
 <211> 74  
 <212> PRT  
 <213> Homo sapiens

<400> 296  
 Ser Lys Thr Gly Ile Val Leu Gln Thr Phe Arg Ala Glu Phe Gln Glu  
 1 5 10 15  
 Leu Lys Ser Glu Lys Gln Gln Ala Ala Phe Pro Lys Arg Tyr Thr Cys  
 20 25 30  
 Phe Gly His Gln Arg Arg Thr Glu Leu Arg Ala Ala Val Glu Asn Leu  
 35 40 45  
 Lys His Ser Ala Glu Phe Leu Ser Ala Pro Leu Ala Asn Lys Leu Lys  
 50 55 60

166

Cys Gln Thr Ala Leu Ala Ala Gly Tyr Phe  
65 70

<210> 297  
<211> 133  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (34)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (60)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (69)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (96)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 297  
Met Ala Pro Ala Gly Cys Cys Cys Cys Cys Cys Phe Trp Gly Gly Ala  
1 5 10 15  
Val Ala Ala Ala Gly Ala Ala Arg Arg Val Leu Leu Leu Leu Leu Leu  
20 25 30  
Gly Xaa Leu Ser Ala Arg Leu Arg Pro Gly Ala Leu Ala Thr Glu His  
35 40 45  
Tyr Ser Pro Leu Ala Leu Leu Lys Gln Glu Leu Xaa His Arg Gln Gln  
50 55 60  
Gln Glu Ala Pro Xaa Gly Gly Gly Gly Cys Ser Pro Gln Ser Gly Asp  
65 70 75 80  
Trp Gly Asp Gln Tyr Ser Ala Glu Cys Gly Glu Ser Ser Phe Leu Xaa  
85 90 95  
Phe His Asp Ser Asp Cys Glu Pro Gln Gly Ser Ser Pro Cys Asp Ser  
100 105 110  
Leu Leu Ser Leu Asn Thr Ala Lys Ile Leu Ser Gln Ala Lys Ser Ile  
115 120 125  
Ala Glu Gln Lys Arg  
130

<210> 298  
<211> 108  
<212> PRT  
<213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (89)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (91)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (102)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (106)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 298

Met	Thr	Ser	Gln	Asn	Leu	Trp	Val	Ile	Val	Val	Ile	Ala	Asn	Ser	Ile
1				5					10					15	

Leu	Val	Ile	Val	Ala	Gln	Tyr	Arg	Asp	Glu	Gly	Asn	Arg	Phe	Cys	Asn
			20					25					30		

Gln	Met	Ile	Leu	Gly	Ser	Glu	Ser	Thr	Leu	Pro	Leu	Thr	Ser	Tyr	Met
		35					40					45			

Thr	Ser	Ser	Asn	Phe	His	His	Leu	Ser	Met	Leu	Gln	Phe	Pro	His	Arg
	50					55					60				

Gln	Asp	Gly	Cys	Gly	Gly	Arg	Gly	Thr	Thr	Val	Gln	Ile	His	His	Pro
65				70						75					80

Lys	Phe	Lys	Met	Leu	Gln	Asn	Leu	Xaa	Arg	Xaa	Trp	Trp	Leu	Ile	Pro
				85					90					95	

Val	Ile	Pro	Ala	Leu	Xaa	Glu	Val	Lys	Xaa	Asp	Gly
			100					105			

&lt;210&gt; 299

&lt;211&gt; 68

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (19)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 299

Asn	Phe	Leu	Glu	Pro	Lys	Cys	Asp	Ala	Thr	Ser	Gly	Lys	Phe	His	Asn
1				5					10					15	

Ser	Ser	Xaa	Val	Ile	Asp	Cys	Ser	Gly	Asn	Ala	Gly	Thr	His	His	Glu
			20					25					30		

Val	Tyr	Ser	Ala	Ser	Ser	Lys	Glu	Ile	Pro	Val	Ser	Ser	Tyr	Ile	Ser
		35					40					45			

Phe	Ser	His	Met	Pro	Asp	Arg	Tyr	Leu	Ser	Ser	Phe	Thr	Val	Arg	Tyr
	50					55						60			

168

Phe Cys Val Glu  
65

<210> 300  
<211> 194  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (168)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 300  
Met Met Trp Leu Leu Leu Thr Thr Thr Cys Leu Ile Cys Gly Thr Leu  
1 5 10 15  
Asn Ala Gly Gly Phe Leu Asp Leu Glu Asn Glu Val Asn Pro Glu Val  
20 25 30  
Trp Met Asn Thr Ser Glu Ile Ile Ile Tyr Asn Gly Tyr Pro Ser Glu  
35 40 45  
Glu Tyr Glu Val Thr Thr Glu Asp Gly Tyr Ile Leu Leu Val Asn Arg  
50 55 60  
Ile Pro Tyr Gly Arg Thr His Ala Arg Ser Thr Gly Pro Arg Pro Val  
65 70 75 80  
Val Tyr Met Gln His Ala Leu Phe Ala Asp Asn Ala Tyr Trp Leu Glu  
85 90 95  
Asn Tyr Ala Asn Gly Ser Leu Gly Phe Leu Leu Ala Asp Ala Gly Tyr  
100 105 110  
Asp Val Trp Met Gly Asn Ser Arg Gly Asn Thr Trp Ser Arg Arg His  
115 120 125  
Lys Thr Leu Ser Glu Thr Asp Glu Lys Phe Trp Ala Phe Ser Phe Asp  
130 135 140  
Glu Met Ala Lys Tyr Asp Leu Pro Gly Val Ile Asp Phe Ile Val Asn  
145 150 155 160  
Lys Thr Gly Gln Glu Lys Leu Xaa Phe Ile Gly His Ser Leu Gly Thr  
165 170 175  
Thr Ile Gly Phe Val Ala Phe Ser Pro Cys Leu Asn Trp His Lys Glu  
180 185 190

Ser Lys

<210> 301  
<211> 87  
<212> PRT  
<213> Homo sapiens

<400> 301  
Met Arg Phe Ile Trp Leu Met Phe Leu Gln Ala Val Gln Ala Ser Gly  
1 5 10 15



169

Lys Gly Leu Arg Lys Leu Pro His Thr Val Glu Asp Glu Gly Glu Pro  
                   20                                  25                                  30  
 Glu Cys Ala Asp Tyr Met Val Arg Glu Trp Lys Gln Glu Arg Gly Ala  
                   35                                  40                                  45  
 Gly Gly Ala Arg Ile Phe Ser Thr Ile Ser Ser Trp Met Ser Thr Val  
                   50                                  55                                  60  
 Ala His Ala Cys Asn Pro Ser Thr Leu Gly Ala Gln Asp Gly Arg Ile  
                   65                                  70                                  75                                  80  
 Thr Ser Ala Gln Glu Phe Asn  
                                   85

<210> 302  
 <211> 90  
 <212> PRT  
 <213> Homo sapiens

<400> 302  
 Met Asp Arg Arg Arg Met Ala Leu Arg Pro Gly Ser Arg Arg Pro Thr  
   1                                  5                                  10                                  15  
 Ala Phe Phe Phe His Ser Arg Trp Leu Val Pro Asn Leu Leu Ala Phe  
                   20                                  25                                  30  
 Phe Leu Gly Leu Ser Gly Ala Gly Pro Ile His Leu Pro Met Pro Trp  
                   35                                  40                                  45  
 Pro Asn Gly Arg Arg His Arg Val Leu Asp Pro His Thr Gln Leu Ser  
                   50                                  55                                  60  
 Thr His Glu Ala Pro Gly Arg Trp Lys Pro Val Ala Pro Arg Arg Met  
                   65                                  70                                  75                                  80  
 Lys Ala Cys Pro Gln Val Leu Leu Glu Trp  
                                   85                                  90

<210> 303  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<400> 303  
 Met Met Ser Ile His Cys Val Gln Pro Leu Leu Pro Leu Phe Leu Pro  
   1                                  5                                  10                                  15  
 Ser Ser Tyr Phe Lys Gln Phe Leu Leu Leu Pro Trp Thr Phe Gly Val  
                   20                                  25                                  30  
 Ala Leu

<210> 304  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

170

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (32)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 304

His	Thr	Phe	Ser	Asn	Cys	Leu	Leu	Glu	Arg	Leu	Tyr	Gln	Ala	Arg	Cys
1				5					10					15	

Ser	Cys	Leu	Met	Pro	Val	Ile	Leu	Ala	Leu	Trp	Glu	Ala	Glu	Xaa	Xaa
		20						25					30		

Gly	Gln	Leu	Glu	Leu	Arg	Ser	Ser	Arg	Pro	Ala	Trp	Ala	Thr	Trp
	35						40					45		

&lt;210&gt; 305

&lt;211&gt; 245

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 305

Met	Phe	Leu	Leu	Phe	Leu	Leu	Thr	Cys	Glu	Leu	Ala	Ala	Glu	Val	Ala
1				5					10					15	

Ala	Glu	Val	Glu	Lys	Ser	Ser	Asp	Gly	Pro	Gly	Ala	Ala	Gln	Glu	Pro
		20						25					30		

Thr	Trp	Leu	Thr	Asp	Val	Pro	Ala	Ala	Met	Glu	Phe	Ile	Ala	Ala	Thr
		35					40					45			

Glu	Val	Ala	Val	Ile	Gly	Phe	Phe	Gln	Asp	Leu	Glu	Ile	Pro	Ala	Val
	50					55					60				

Pro	Ile	Leu	His	Ser	Met	Val	Gln	Lys	Phe	Pro	Gly	Val	Ser	Phe	Gly
65					70					75					80

Ile	Ser	Thr	Asp	Ser	Glu	Val	Leu	Thr	His	Tyr	Asn	Ile	Thr	Gly	Asn
				85					90					95	

Thr	Ile	Cys	Leu	Phe	Arg	Leu	Val	Asp	Asn	Glu	Gln	Leu	Asn	Leu	Glu
			100					105					110		

Asp	Glu	Asp	Ile	Glu	Ser	Ile	Asp	Ala	Thr	Lys	Leu	Ser	Arg	Phe	Ile
		115					120					125			

Glu	Ile	Asn	Ser	Leu	His	Met	Val	Thr	Glu	Tyr	Asn	Pro	Val	Ala	Ser
	130					135					140				

Pro	Glu	Tyr	Glu	Glu	Asn	Met	His	Arg	Tyr	Gln	Lys	Ala	Ala	Lys	Leu
145					150					155					160

Phe	Gln	Gly	Lys	Ile	Leu	Phe	Ile	Leu	Val	Asp	Ser	Gly	Met	Lys	Glu
			165						170					175	

Asn	Gly	Lys	Val	Ile	Ser	Phe	Phe	Lys	Leu	Lys	Glu	Ser	Gln	Leu	Pro
			180					185					190		

Ala	Leu	Ala	Ile	Tyr	Gln	Thr	Leu	Asp	Asp	Glu	Trp	Asp	Thr	Leu	Pro
		195					200					205			

171

Thr Ala Glu Val Ser Val Glu His Val Gln Asn Phe Cys Asp Gly Phe  
 210 215 220  
 Leu Ser Gly Lys Leu Leu Lys Glu Asn Arg Glu Ser Glu Gly Lys Thr  
 225 230 235 240  
 Pro Lys Val Glu Leu  
 245

<210> 306  
 <211> 140  
 <212> PRT  
 <213> Homo sapiens

<400> 306  
 Met Phe Pro Leu His Leu Ala Val Leu Phe Gly Phe Ser Asp Cys Cys  
 1 5 10 15  
 Arg Lys Leu Leu Ser Ser Gly Gln Leu Tyr Ser Ile Val Ser Ser Leu  
 20 25 30  
 Ser Asn Glu His Val Leu Ser Ala Gly Phe Asp Ile Asn Thr Pro Asp  
 35 40 45  
 Asn Leu Gly Arg Thr Cys Leu His Ala Ala Ala Ser Gly Gly Asn Val  
 50 55 60  
 Glu Cys Leu Asn Leu Leu Leu Ser Ser Gly Ala Asp Leu Arg Arg Arg  
 65 70 75 80  
 Asp Lys Phe Gly Arg Thr Pro Leu His Tyr Ala Ala Ala Asn Gly Ser  
 85 90 95  
 Tyr Gln Cys Ala Val Thr Leu Val Thr Ala Gly Ala Gly Val Asn Glu  
 100 105 110  
 Ala Asp Cys Lys Gly Cys Ser Pro Leu His Tyr Ala Ala Ala Ser Asp  
 115 120 125  
 Thr Tyr Arg Arg Ala Glu Pro His Thr Pro Ser Ser  
 130 135 140

<210> 307  
 <211> 110  
 <212> PRT  
 <213> Homo sapiens

<400> 307  
 Met Lys Arg Tyr Ile Ile Ser Leu Gln Ser Pro Leu Ser His Ser Ser  
 1 5 10 15  
 Met Trp Pro Ala Tyr Leu Leu Pro Ile Met Leu Leu Ile His Leu Gln  
 20 25 30  
 Ala Ile Cys His Gln Ile Lys Lys Gln Gln Thr Glu Gly Gln Ser Gln  
 35 40 45  
 Asp Val Leu Thr His His Cys Asn Phe Leu Leu Glu Met Ile Pro Phe  
 50 55 60  
 Arg Lys Arg Leu Val Glu Ile Gly Val Lys Gly Thr Leu Gln Ile Ser

:172

65		70		75		80									
Pro	Val	Leu	Ser	Tyr	Phe	Gln	Leu	Tyr	Arg	Gln	Glu	Gln	Phe	Lys	Ser
				85					90					95	
Lys	Glu	Phe	Ser	Arg	Phe	Leu	Gln	Cys	His	Lys	Ala	Val	Ser		
			100					105					110		

<210> 308  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 308  
 Met Pro Pro Pro Phe Leu Arg Lys Pro Leu Ile Leu Cys Val Phe Leu  
 1 5 10 15  
 Pro Thr Glu Gly Asn Cys Gly Gly Ser Ser Leu Ala Phe Leu Leu Asn  
 20 25 30  
 Phe Ala Gly Asn Ser Pro Gln Phe Leu Ser Glu Val Arg Thr Val His  
 35 40 45  
 Tyr Gln Arg Asp Trp Thr Leu Tyr Pro Leu Ala Lys Trp Glu Lys Ile  
 50 55 60  
 Leu Pro Ala His Ser Thr Pro Pro Trp Pro Ser Pro Thr Pro His Pro  
 65 70 75 80  
 Gln Gln His Phe His Gly Asn Pro Asp Gly Arg Val Val Leu Trp Leu  
 85 90 95  
 Ser Cys Asp Arg Leu Ala Phe Ile Leu Glu Ser  
 100 105

<210> 309  
 <211> 251  
 <212> PRT  
 <213> Homo sapiens

<400> 309  
 Met Gly Pro Pro Gly Ala Gly Val Ser Cys Arg Gly Gly Cys Gly  
 1 5 10 15  
 Phe Ser Arg Leu Leu Ala Trp Cys Phe Leu Leu Ala Leu Ser Pro Gln  
 20 25 30  
 Ala Pro Gly Ser Arg Gly Ala Glu Ala Val Trp Thr Ala Tyr Leu Asn  
 35 40 45  
 Val Ser Trp Arg Val Pro His Thr Gly Val Asn Arg Thr Val Trp Glu  
 50 55 60  
 Leu Ser Glu Glu Gly Val Tyr Gly Gln Asp Ser Pro Leu Glu Pro Val  
 65 70 75 80  
 Ala Gly Val Leu Val Pro Pro Asp Gly Pro Gly Ala Leu Asn Ala Cys  
 85 90 95  
 Asn Pro His Thr Asn Phe Thr Val Pro Thr Val Trp Gly Ser Thr Val  
 100 105 110

173

Gln Val Ser Trp Leu Ala Leu Ile Gln Arg Gly Gly Gly Cys Thr Phe  
 115 120 125  
 Ala Asp Lys Ile His Leu Ala Tyr Glu Arg Gly Ala Ser Gly Ala Val  
 130 135 140  
 Ile Phe Asn Phe Pro Gly Thr Arg Asn Glu Val Ile Pro Met Ser His  
 145 150 155 160  
 Pro Gly Ala Val Asp Ile Val Ala Ile Met Ile Gly Asn Leu Lys Gly  
 165 170 175  
 Thr Lys Ile Leu Gln Ser Ile Gln Arg Gly Ile Gln Val Thr Met Val  
 180 185 190  
 Ile Glu Val Gly Lys Lys His Gly Pro Trp Val Asn His Tyr Ser Ile  
 195 200 205  
 Phe Phe Arg Phe Cys Val Leu Phe Tyr Tyr Tyr Gly Gly Asn Cys Gly  
 210 215 220  
 Leu Phe Tyr Leu Leu Phe Cys Ser Lys Ala Thr Glu Cys Lys Ser Ser  
 225 230 235 240  
 Lys Gln Glu Ala Glu Ala Ile Lys Gly Arg Cys  
 245 250

<210> 310  
 <211> 124  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (78)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (108)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (111)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 310  
 Met Leu Thr Gln Ser Gln Gln Val Leu Arg Gly Ile Leu Leu Phe Leu  
 1 5 10 15  
 Gln Asn Ile Leu Gln Val Ser Trp Gly Ser Pro Leu Ala Leu Ala Ser  
 20 25 30  
 Pro Pro Ser Pro Ser Leu Gln Pro Gly Asn Gly Leu Ala Ser Ser Leu  
 35 40 45  
 Leu Ala Leu Gln Pro Gly Leu Ala Gly Pro Trp Ala Gly Pro Gln Glu  
 50 55 60  
 Pro Ser Pro Ala Met Cys Phe Pro Lys Lys Arg Ser Leu Xaa Pro Asn  
 65 70 75 80  
 Leu Arg Lys Gln Trp Ala Ser Ile His Ile Asn Asp Pro Arg Gly Thr

174

	85		90		95
Leu Cys Pro Arg Cys Thr Gly Cys Asn Gln Arg Xaa Ser Gly Xaa Ser					
100		105		110	
Gly Leu Ile Trp Arg Asp Arg Phe Tyr His His Pro					
115		120			

<210> 311  
 <211> 87  
 <212> PRT  
 <213> Homo sapiens

<400> 311  
 Met Thr Trp Ser Phe Cys Phe Ala Leu Phe Cys Phe Val Leu Phe Phe  
 1 5 10 15  
 Ala Ala Ser Leu Ile Gly Tyr Ile Leu Leu Pro Ser Ala Ser Pro Arg  
 20 25 30  
 Asn His Arg Arg Pro Asn Asn Glu Ala Arg Val Gly Thr Pro Gly Gln  
 35 40 45  
 Leu Asp Asp Glu Leu Lys Gly Arg Gln Pro Leu Ala Ser Arg Leu Glu  
 50 55 60  
 Thr Ser Gln Cys Thr Gln Gly Leu Leu Ala Ser Arg Pro Ser Gly Val  
 65 70 75 80  
 Ser Lys Ala Leu Leu Tyr Pro  
 85

<210> 312  
 <211> 84  
 <212> PRT  
 <213> Homo sapiens

<400> 312  
 Met Glu Trp Gln Phe Gly Lys Pro Ser Phe Leu Leu Ser Leu Leu Met  
 1 5 10 15  
 Leu Leu Val Leu Glu Trp Lys Ala Leu Cys Gly Val Arg Leu Gly His  
 20 25 30  
 Leu Gly Leu Gln Val Pro Asn Pro Ser Leu Lys Ser Thr Cys Leu Trp  
 35 40 45  
 Pro Leu Arg Ser Leu Cys Pro Trp Arg Leu Tyr Pro Ile Lys Ile Met  
 50 55 60  
 Ile Ser Leu Pro Leu Pro Ser Leu Gln Leu Pro Ser Ser Pro His Arg  
 65 70 75 80  
 Pro Phe Gln Leu

<210> 313  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (4)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (10)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 313  
 Leu Pro Gly Xaa Cys Phe Asn His Leu Xaa Ile Asn Phe Trp Lys Lys  
           1                  5                  10                  15  
 Ile Ile Ile Phe Thr Leu Lys Phe Pro Tyr Ser Lys Tyr Ser Ile Ser  
                   20                  25                  30  
 Val Trp Gln Met Asp Glu Trp Ala Asp Ile Ile Gly Ser Tyr His Val  
           35                  40                  45  
 Asp Tyr Glu Glu Val Gln Ser Ile Gln Asn Lys Asn Thr Lys His Ser  
           50                  55                  60  
 Asn Lys Pro Arg Val Cys Gln  
           65                  70

<210> 314  
 <211> 142  
 <212> PRT  
 <213> Homo sapiens

<400> 314  
 Met Leu Trp Thr Thr Leu Thr Gly Val Ser Leu Ala Leu Phe Pro Val  
           1                  5                  10                  15  
 Ala Gln Ala Pro Thr Ala Leu Val Ala Leu Ala Val Ala Tyr Gly Phe  
                   20                  25                  30  
 Thr Ser Gly Ala Leu Ala Pro Leu Ala Phe Ser Val Leu Pro Glu Leu  
           35                  40                  45  
 Ile Gly Thr Arg Arg Ile Tyr Cys Gly Leu Gly Leu Leu Gln Met Ile  
           50                  55                  60  
 Glu Ser Ile Gly Gly Leu Leu Gly Pro Pro Leu Ser Gly Tyr Leu Arg  
           65                  70                  75                  80  
 Asp Val Thr Gly Asn Tyr Thr Ala Ser Phe Val Val Ala Gly Ala Phe  
                   85                  90                  95  
 Leu Leu Ser Gly Ser Gly Ile Leu Leu Thr Leu Pro His Phe Phe Cys  
           100                  105                  110  
 Phe Ser Thr Thr Thr Ser Gly Pro Gln Asp Leu Val Thr Glu Ala Leu  
           115                  120                  125  
 Asp Thr Lys Val Pro Leu Pro Lys Glu Gly Leu Glu Glu Asp  
           130                  135                  140

<210> 315  
 <211> 84

176

<212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (19)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 315  
 Met Phe Leu Ser Gly Lys Pro Gly Glu Ser Tyr Leu Ser His Leu Pro  
   1                  5                  10                  15  
 Cys Leu Xaa Phe Phe Phe Phe Phe Phe Gly Trp Ser Cys Cys Leu Asp  
                   20                  25                  30  
 Asp Ala Phe Thr Met Gln Glu Arg Val Phe Val Lys Asp Ile Phe Glu  
           35                  40                  45  
 Asp Trp Leu Phe His Ile Val Leu His Ser Leu Thr Val Ala Lys Cys  
   50                  55                  60  
 Thr Val Asp Phe His Asp His Cys Ile Phe Leu Val Ile Glu Met Tyr  
   65                  70                  75                  80  
 Leu Leu Cys Phe

<210> 316  
 <211> 88  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 316  
 Met Phe Pro Ile Leu Ser Ile Thr Thr Leu Ser Ile Leu Ala Phe Phe  
   1                  5                  10                  15  
 Leu Trp Leu Ser Val Thr Ser His Phe Tyr Arg Gln Lys Thr Gly Phe  
                   20                  25                  30  
 His His Ser Pro Ser Phe Tyr Leu Ile Val Gln Ile Trp Asp Thr Tyr  
   35                  40                  45  
 Ala Asp Ile Val Ala Ser Glu Tyr Val Phe Pro Trp Arg Xaa Thr Leu  
   50                  55                  60  
 Ser Ser Arg Glu Gln Cys Leu Ser Val Val Pro Val Ala Phe Ser Leu  
   65                  70                  75                  80  
 Ile Asp Phe Ile Ser Lys Val Ser  
                   85

<210> 317  
 <211> 127  
 <212> PRT  
 <213> Homo sapiens

<400> 317



177

Met Met Pro Thr Tyr Ala Ile Cys Met Val Leu Val Phe Leu Leu Leu  
 1 5 10 15  
 Val His Leu His Ile Ile Asn Thr Asn Thr His Thr His Thr His Thr  
 20 25 30  
 His Thr His Thr Gly Leu Leu Pro Glu Pro Tyr Met Leu Tyr Phe Gln  
 35 40 45  
 Phe Leu Ser Val Leu Arg Gly Tyr Ile Leu Ser Arg Trp Thr Asp Arg  
 50 55 60  
 Glu Tyr Thr Trp Ile Ser Thr Lys Ile Tyr Ser Pro Asn Ser Pro Glu  
 65 70 75 80  
 Pro Pro Ala Ser Cys Pro Ser Pro Thr Gln Ser Ile Ser Arg His Ala  
 85 90 95  
 Val Gln Gly Ser Thr Phe Leu Lys Ala Gln Leu Pro Thr Ser Glu Gln  
 100 105 110  
 Val Gln Ile His Pro Leu His Pro Pro Ile His Leu Ser Pro Leu  
 115 120 125

&lt;210&gt; 318

&lt;211&gt; 83

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 318

Met Thr Ser Leu Ala Arg Leu Pro Cys Ser Tyr Leu Cys Leu Pro Cys  
 1 5 10 15  
 Gln Leu Ser Ser Cys Cys Ala Phe Ser Gln Pro Ile Ser Ala Leu Leu  
 20 25 30  
 Pro Ser Pro Ser Thr Pro Val Leu Leu Ser Ala Pro Arg Pro Ser Ser  
 35 40 45  
 Gln Gly Val Pro Gly Thr Arg Ser Glu Phe Pro Ser Thr Pro Phe Cys  
 50 55 60  
 Leu Pro Ser Phe Pro Arg Glu Ser Phe Leu Asp Ser Phe His Leu Val  
 65 70 75 80  
 Ser Ser His

&lt;210&gt; 319

&lt;211&gt; 86

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (64)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (66)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

178

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (75)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 319

Met Ala Lys Ala Pro Phe Tyr His Leu Leu Phe Cys Phe Gly Ile Trp  
1 5 10 15Ser Asp Ser Tyr Ser Ser Leu Gly Leu Ala Gln Trp Arg Asn Trp Cys  
20 25 30Ser Tyr Cys Thr Gly Leu Cys Thr Pro Cys Asn Cys Asp Val Tyr Asp  
35 40 45Cys Ser Ser Cys Phe Pro Ile Leu His Phe Gln Ser Pro Arg Ala Xaa  
50 55 60Leu Xaa Arg Ile Thr Ser Thr Val Asn His Xaa Arg Asp Cys Thr Thr  
65 70 75 80Arg His Val Gly Gly Lys  
85

&lt;210&gt; 320

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (13)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (21)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 320

Ile Xaa Gly Glu Pro Arg Phe Leu Gly Thr Met Pro Xaa Leu Glu Phe  
1 5 10 15Gly Ser Pro Pro Xaa Xaa Phe Gln Ala Gly Pro Glu Leu Pro Glu Asn  
20 25 30Asn Ser Gly Gln Leu Thr Thr Ser Asp Ser Ser Pro Pro Asn Met Ala  
35 40 45Tyr Pro Cys Ser Ser Asp Val Ile Leu Val Ala Ser Val Asn Ser Val  
50 55 60

Cys His Ala Val Gln Thr

65

70

<210> 321  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (40)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (42)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (53)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 321  
 Met Arg Trp Arg Lys Pro Leu Cys Leu Trp Cys Leu Leu Thr Gln Gly  
           1                  5                  10                  15

Glu Thr Glu Ala Gln Ala Gly Gln Pro Leu Ala Trp Gly Gly Gly Trp  
                   20                  25                  30

Val Val Leu Arg Pro Val Thr Xaa Pro Xaa Gln His Pro Pro Val Asp  
           35                  40                  45

Pro Leu Pro Ala Xaa Ala Arg Pro Glu Ser Cys Ser Gln Ala Gln Thr  
           50                  55                  60

Leu Ala Cys Pro Ser Gly Asp Ala Gly Gln Tyr Ser Ser Leu Gln Pro  
           65                  70                  75                  80

Ser

<210> 322  
 <211> 2  
 <212> PRT  
 <213> Homo sapiens

<400> 322  
 Arg Ala  
       1

<210> 323  
 <211> 138  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (137)  
 <223> Xaa equals any of the naturally occurring L-amino acids

180

&lt;400&gt; 323

Met Thr Ser Gly Pro Arg Gly Val Val His Phe Tyr Gly Tyr Ser Val  
 1 5 10 15

Val Ser Thr Leu Ala Leu Leu Val Ser Ile Ala Phe Pro Ile Pro Ile  
 20 25 30

Cys Gln Gln Trp Glu Pro Ser Tyr Lys Arg Val Lys Ala Leu Ser Ile  
 35 40 45

Val Gly Gly Asp Pro His Leu Ile Leu Leu Ala Ser Thr Thr Val Leu  
 50 55 60

Val Gly Ala Ile Val Ser Thr Val Gln Asn Phe Leu Phe Trp His Met  
 65 70 75 80

Lys Asp His Gly Ser Gly Glu Leu Val Met Gly Phe Ser Val Ala Leu  
 85 90 95

Ser Leu Leu Gly Glu Ile Leu Leu His Pro Phe Lys Ala Thr Leu Leu  
 100 105 110

Arg Lys Leu Ser Arg Thr Gly Leu Val Gly Leu Gly Leu Ser Cys Leu  
 115 120 125

Ala Gly Gln Leu Leu Tyr Tyr Ser Xaa Leu  
 130 135

&lt;210&gt; 324

&lt;211&gt; 124

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (66)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (102)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (104)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (106)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (109)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (111)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

<221> SITE  
 <222> (114)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (115)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (122)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 324  
 Met Ala Ser Pro Ala Pro Ala Cys Leu Gly Ser Leu Leu Ser Trp Thr  
   1                  5                 10                 15  
 Val Cys Gly Trp Gly Glu Val Val Ser Gly Pro Pro Cys Ala Val Ser  
                  20                 25                 30  
 Ala Trp Gly Cys Ser Trp Ala Thr Trp Val Thr Pro Ser Val Val Val  
          35                 40                 45  
 Gln Leu Ala Pro Ser Gly Ala Val Gln Thr Pro Leu Ser Pro Glu Leu  
   50                 55                 60  
 Leu Xaa Ile Ser Phe Gln Leu His Ala Ala Pro Leu Gly Gln Phe Tyr  
   65                 70                 75                 80  
 Phe Pro Ile Leu Gln Met Gly Lys Glu Lys Leu Arg Leu Arg Asn Met  
                  85                 90                 95  
 Pro Lys Glu Ala Pro Xaa Pro Xaa Phe Xaa Leu Phe Xaa Leu Xaa Leu  
          100                 105                 110  
 Arg Xaa Xaa Leu Cys His Pro Gly Trp Xaa Ala Gly  
      115                 120

<210> 325  
 <211> 82  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (63)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (75)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (76)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (77)  
 <223> Xaa equals any of the naturally occurring L-amino acids

182

&lt;400&gt; 325

Met Gly Gln Leu Cys His Ser Pro Ser Cys Leu Pro Ser Gly Ala Phe  
 1 5 10 15  
 Cys Leu Leu Leu Ser Ser Val Leu Gly Ile Ile Val Leu Asn Ser Thr  
 20 25 30  
 Asp Thr Ile Ser Ser Ser His Pro Pro Leu Ser Ser Asn Leu Pro Ser  
 35 40 45  
 Trp Gly Tyr Thr Thr Thr Lys Ala His Leu Ser Leu Gly Leu Xaa Gly  
 50 55 60  
 Phe Ala Gly Lys Glu Asn Met Lys Glu Leu Xaa Xaa Xaa Ser Ser Arg  
 65 70 75 80  
 Ser Phe

&lt;210&gt; 326

&lt;211&gt; 248

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (51)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 326

Met Thr Leu Leu Ser Leu Leu Gly Arg Ile Met Arg Tyr Phe Leu Leu  
 1 5 10 15  
 Arg Pro Glu Thr Leu Phe Leu Leu Cys Ile Ser Leu Ala Leu Trp Ser  
 20 25 30  
 Tyr Phe Phe His Thr Asp Glu Val Lys Thr Ile Val Lys Ser Ser Arg  
 35 40 45  
 Asp Ala Xaa Lys Met Val Lys Gly Lys Val Ala Glu Ile Met Gln Asn  
 50 55 60  
 Asp Arg Leu Gly Gly Leu Asp Val Leu Glu Ala Glu Phe Ser Lys Thr  
 65 70 75 80  
 Trp Glu Phe Lys Asn His Asn Val Ala Val Tyr Ser Ile Gln Gly Arg  
 85 90 95  
 Arg Asp His Met Glu Asp Arg Phe Glu Val Leu Thr Asp Leu Ala Asn  
 100 105 110  
 Lys Thr His Pro Ser Ile Phe Gly Ile Phe Asp Gly His Gly Gly Glu  
 115 120 125  
 Thr Ala Ala Glu Tyr Val Lys Ser Arg Leu Pro Glu Ala Leu Lys Gln  
 130 135 140  
 His Leu Gln Asp Tyr Glu Lys Asp Lys Glu Asn Ser Val Leu Ser Tyr  
 145 150 155 160  
 Gln Thr Ile Leu Glu Gln Gln Ile Leu Ser Ile Asp Arg Glu Met Leu  
 165 170 175  
 Glu Lys Leu Thr Val Ser Tyr Asp Glu Ala Gly Thr Thr Cys Leu Ile

183

180	185	190
Ala Leu Leu Ser Asp Lys Asp Leu Thr Val Ala Asn Val Gly Asp Ser		
195	200	205
Arg Gly Val Leu Cys Asp Lys Asp Gly Asn Ala Ile Pro Leu Ser His		
210	215	220
Asp His Lys Pro Tyr Gln Leu Lys Glu Arg Lys Arg Ile Lys Arg Ala		
225	230	235
240		
Gly Gly Phe Ile Ser Phe Asn Gly		
245		

<210> 327  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 327  
 Phe Leu Ile Ala Leu Asp Leu Leu Asn Val Phe Cys Leu Leu Leu Ser  
     1                    5                    10                    15  
 Val Phe Ser Leu Glu Ile Glu Cys Lys Pro Tyr  
                     20                    25

<210> 328  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<400> 328  
 Met Lys Ser Lys Phe Cys Phe Ala Ser Pro Met Arg Leu Pro Lys Ala  
     1                    5                    10                    15  
 Leu Leu Ala Phe Ser Ala Cys Trp Gln Leu Leu Ser Ala Trp Leu Leu  
                     20                    25                    30  
 His Leu Ser Pro His Thr Ala Tyr Lys Ser Glu Lys Val Ser Arg Ile  
                     35                    40                    45  
 Lys Ala Lys  
     50

<210> 329  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (20)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 329  
 Met Pro Asn Ser Leu Leu Gly Val Phe Phe Cys Phe Val Leu Phe Cys  
     1                    5                    10                    15  
 Phe Val Leu Xaa Cys Leu Ile Gln Ser Phe Thr Leu Ser Pro Arg Leu  
                     20                    25                    30

Glu

<210> 330  
 <211> 99  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (4)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (9)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (16)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (86)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 330  
 Gln Lys Ala Xaa Trp Ser Gln Leu Xaa Pro Ile Tyr Leu Thr Val Xaa  
   1                  5                  10                  15  
 Ile Phe Gln Arg Gln Phe Gln Gly Tyr Tyr Ser His Asp Ser Thr His  
                   20                  25                  30  
 Pro Gln Gly Val Arg Phe Ser Leu Cys Lys Cys Ile Met Thr Phe Tyr  
           35                  40                  45  
 Asn Thr Pro Cys His Ala Leu Phe Tyr Pro Ala Arg Ile Gly Val Trp  
   50                  55                  60  
 Pro Gln Leu Val Pro Thr Ser Ser Thr Ala Ile Thr Ser Ser Ser Ser  
   65                  70                  75                  80  
 Ala Pro Ser Val Val Xaa Glu Pro Leu Val Ser Ser Glu Met His Met  
                   85                  90                  95

Leu Lys Ser

<210> 331  
 <211> 35  
 <212> PRT  
 <213> Homo sapiens

<400> 331  
 Met Cys His His Ala Gln Leu Ile Phe Val Leu Leu Val Glu Thr Gly  
   1                  5                  10                  15  
 Phe Cys His Val Gly Gln Ala Gly Leu Glu Leu Leu Thr Ser His Asp  
           20                  25                  30



185

Leu Arg Thr  
35

<210> 332  
<211> 262  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (154)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 332  
His Gly Pro Pro Glu Gly Ala Val Gly Cys Gln Arg Glu Gln Gln Arg  
1 5 10 15  
Gln Ala Ala Ala Gln Pro Arg Gln His Gln Ala Ile Arg Ser Val Gly  
20 25 30  
Arg Gln Pro Val Val Cys Cys Pro Gln Thr Leu Asp Ala Gly Leu Gly  
35 40 45  
Pro Gly His Ala Ala Val Ala Arg Pro Leu Leu Arg Pro Leu Gln Val  
50 55 60  
Gly Glu Ala Glu Cys Gly His Gly Gln Gln Gly Gly Gln Asp Pro Ala  
65 70 75 80  
Gly Ser Ala His Gly Pro Gly Val Leu Gly Ser Gln Val Ala Ser Gly  
85 90 95  
Glu Glu Gly Val His Asp Ala Gln Val Ala Val Glu Ala Asp Ala Gly  
100 105 110  
Asp Glu Asp Asp Ala Ala Gln Gln Val Ala Gly Glu Glu Glu Ala Leu  
115 120 125  
Gln Ala Ala Arg Gly Leu Pro Ile Ala Pro Val Leu Gly Gly Ile Glu  
130 135 140  
Val Gly Gly Gln Arg Gly Gln Arg Gln Xaa Ala Glu Gln Val Ala Asp  
145 150 155 160  
Cys Gln Leu Asp Arg Glu Asp His Gly Gly Val Pro Trp Ala Leu Leu  
165 170 175  
Pro Asp Ala Glu Ala Val Gln Gly Gln Ala Ile Ala Gly His Gly His  
180 185 190  
Gln Glu Leu Asn His Gln Tyr Gly Pro Gln Glu Val Pro Leu Glu Pro  
195 200 205  
Thr Glu Phe Val Val Gly Ser Cys Gln Glu Val Gly Arg Ala Gly Leu  
210 215 220  
Gly Thr Arg Asp Val Gly Cys His Ala Pro Val Pro Ile Leu Ser Leu  
225 230 235 240  
Cys Leu Leu Pro Ser Ser Pro Ala Pro Pro Pro Val Thr Ser Gly Leu  
245 250 255  
Val Gly Pro Ala Pro Ala

186

260

<210> 333  
 <211> 82  
 <212> PRT  
 <213> Homo sapiens

<400> 333  
 Met Leu Thr Asn Arg Ala Pro Ser Ser Phe Val Trp Phe Leu Cys Leu  
   1                  5                  10                  15  
 Ala Cys His Leu Pro Ser Cys Pro Ser Ala Thr Glu Glu Phe Ala Val  
                   20                  25                  30  
 Phe Ile Pro Lys Tyr His Ser Ser Arg Met Gly Ala Ala Pro Cys His  
                   35                  40                  45  
 Val Leu Gly His Gly Gly Ile Lys Gly Asn Thr Cys Gln Asp Asn Ala  
           50                  55                  60  
 Gly Tyr Asp Phe Cys Arg Pro Leu Gly Leu Ala Ser Phe Leu Lys Arg  
   65                  70                  75                  80  
 Gln Asp

<210> 334  
 <211> 587  
 <212> PRT  
 <213> Homo sapiens

<400> 334  
 Met Arg Pro Arg Gly Leu Pro Pro Leu Leu Val Val Leu Leu Gly Cys  
   1                  5                  10                  15  
 Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr  
                   20                  25                  30  
 Glu Gly Leu Asn Ser Thr Glu Ala Ala Leu Ala Thr Phe Gly Thr Phe  
                   35                  40                  45  
 Pro Ser Thr Arg Pro Pro Gly Thr Pro Arg Ala Pro Gly Pro Ser Ser  
           50                  55                  60  
 Gly Pro Arg Pro Thr Pro Val Thr Asp Val Ala Val Leu Cys Val Cys  
   65                  70                  75                  80  
 Asp Leu Ser Pro Ala Gln Cys Asp Ile Asn Cys Cys Cys Asp Pro Asp  
                   85                  90                  95  
 Cys Ser Ser Val Asp Phe Ser Val Phe Ser Ala Cys Ser Val Pro Val  
                   100                  105                  110  
 Val Thr Gly Asp Ser Gln Phe Cys Ser Gln Lys Ala Val Ile Tyr Ser  
           115                  120                  125  
 Leu Asn Phe Thr Ala Asn Pro Pro Gln Arg Val Phe Glu Leu Val Asp  
           130                  135                  140  
 Gln Ile Asn Pro Ser Ile Phe Cys Ile His Ile Thr Asn Tyr Lys Pro  
   145                  150                  155                  160

187

Ala Leu Ser Phe Ile Asn Pro Glu Val Pro Asp Glu Asn Asn Phe Asp  
 165 170 175  
 Thr Leu Met Lys Thr Ser Asp Gly Phe Thr Leu Asn Ala Glu Ser Tyr  
 180 185 190  
 Val Ser Phe Thr Thr Lys Leu Asp Ile Pro Thr Ala Ala Lys Tyr Glu  
 195 200 205  
 Tyr Gly Val Pro Leu Gln Thr Ser Asp Ser Phe Leu Arg Phe Pro Ser  
 210 215 220  
 Ser Leu Thr Ser Ser Leu Cys Thr Asp Asn Asn Pro Ala Ala Phe Leu  
 225 230 235 240  
 Val Asn Gln Ala Val Lys Cys Thr Arg Lys Ile Asn Leu Glu Gln Cys  
 245 250 255  
 Glu Glu Ile Glu Ala Leu Ser Met Ala Phe Tyr Ser Ser Pro Glu Ile  
 260 265 270  
 Leu Arg Val Pro Asp Ser Arg Lys Lys Val Pro Ile Thr Val Gln Ser  
 275 280 285  
 Ile Val Ile Gln Ser Leu Asn Lys Thr Leu Thr Arg Arg Glu Asp Thr  
 290 295 300  
 Asp Val Leu Gln Pro Thr Leu Val Asn Ala Gly His Phe Ser Leu Cys  
 305 310 315 320  
 Val Asn Val Val Leu Glu Val Lys Tyr Ser Leu Thr Tyr Thr Asp Ala  
 325 330 335  
 Gly Glu Val Thr Lys Ala Asp Leu Ser Phe Val Leu Gly Thr Val Ser  
 340 345 350  
 Ser Val Val Val Pro Leu Gln Gln Lys Phe Glu Ile His Phe Leu Gln  
 355 360 365  
 Glu Asn Thr Gln Pro Val Pro Leu Ser Gly Asn Pro Gly Tyr Val Val  
 370 375 380  
 Gly Leu Pro Leu Ala Ala Gly Phe Gln Pro His Lys Gly Ser Gly Ile  
 385 390 395 400  
 Ile Gln Thr Thr Asn Arg Tyr Gly Gln Leu Thr Ile Leu His Ser Thr  
 405 410 415  
 Thr Glu Gln Asp Cys Leu Ala Leu Glu Gly Val Arg Thr Pro Val Leu  
 420 425 430  
 Phe Gly Tyr Thr Met Gln Ser Gly Cys Lys Leu Arg Leu Thr Gly Ala  
 435 440 445  
 Leu Pro Cys Gln Leu Val Ala Gln Lys Val Lys Ser Leu Leu Trp Gly  
 450 455 460  
 Gln Gly Phe Pro Asp Tyr Val Ala Pro Phe Gly Asn Ser Gln Ala Gln  
 465 470 475 480  
 Asp Met Leu Asp Trp Val Pro Ile His Phe Ile Thr Gln Ser Phe Asn  
 485 490 495  
 Arg Lys Asp Ser Cys Gln Leu Pro Gly Ala Leu Val Ile Glu Val Lys  
 500 505 510

188

Trp Thr Lys Tyr Gly Ser Leu Leu Asn Pro Gln Ala Lys Ile Val Asn  
 515 520 525

Val Thr Ala Asn Leu Ile Ser Ser Ser Phe Pro Glu Ala Asn Ser Gly  
 530 535 540

Asn Glu Arg Thr Ile Leu Ile Ser Thr Ala Val Thr Phe Val Asp Val  
 545 550 555 560

Ser Ala Pro Ala Glu Ala Gly Phe Arg Ala Pro Pro Ala Ile Asn Ala  
 565 570 575

Arg Leu Pro Phe Asn Phe Phe Phe Pro Phe Val  
 580 585

<210> 335  
 <211> 337  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (173)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (255)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (320)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 335  
 Met Gly Leu Ile Val Val Leu Leu Phe Pro Asn Leu Cys Met Cys Thr  
 1 5 10 15

Phe His Ala Gly Gly Phe Gln Cys Val Leu Trp Met Ala Gly Leu Lys  
 20 25 30

Arg Arg Val Pro Leu His Ser Leu Arg Tyr Phe Ile Ser Met Val Gly  
 35 40 45

Leu Phe Ser Lys Pro Gly Leu Leu Pro Trp Tyr Ala Arg Asn Pro Pro  
 50 55 60

Gly Trp Ser Gln Leu Phe Leu Gly Thr Val Cys Lys Gly Asp Phe Thr  
 65 70 75 80

Arg Val Ile Ala Thr Lys Cys Gln Lys Gly Gln Lys Ser Gln Lys Lys  
 85 90 95

Pro Ser His Leu Gly Pro Leu Asp Gly Ser Trp Gln Glu Arg Leu Ala  
 100 105 110

Asp Val Val Thr Pro Leu Trp Arg Leu Ser Tyr Glu Glu Gln Leu Lys  
 115 120 125

Val Lys Phe Ala Ala Gln Lys Lys Ile Leu Gln Arg Leu Glu Ser Tyr  
 130 135 140

189

Ile Gln Met Leu Asn Gly Val Ser Val Thr Thr Ala Val Pro Lys Ser  
 145 150 155 160  
 Glu Arg Leu Ser Cys Leu Leu His Pro Ile Ile Pro Xaa Pro Val Ile  
 165 170 175  
 Asn Gly Tyr Arg Asn Lys Ser Thr Phe Ser Val Asn Arg Gly Pro Asp  
 180 185 190  
 Gly Asn Pro Lys Thr Val Gly Phe Tyr Leu Gly Thr Trp Arg Asp Gly  
 195 200 205  
 Asn Val Val Cys Val Gln Ser Asn His Leu Lys Asn Ile Pro Glu Lys  
 210 215 220  
 His Ser Gln Val Ala Gln Tyr Tyr Glu Val Phe Leu Arg Gln Ser Pro  
 225 230 235 240  
 Leu Glu Pro Cys Leu Val Phe His Glu Gly Gly Tyr Trp Arg Xaa Leu  
 245 250 255  
 Thr Val Arg Thr Asn Ser Gln Gly His Thr Met Ala Ile Ile Thr Phe  
 260 265 270  
 His Pro Gln Lys Leu Ser Gln Glu Glu Leu His Val Gln Lys Glu Ile  
 275 280 285  
 Val Lys Glu Phe Phe Ile Lys Arg Ser Trp Ser Ser Leu Trp Leu Asp  
 290 295 300  
 Leu Thr Leu Leu Pro Gly Lys Tyr His Asp Pro Leu Gln Pro Ser Xaa  
 305 310 315 320  
 Val Ser Leu Ser Ser Phe Cys Leu Gly Asn Leu His Leu Leu Lys Asn  
 325 330 335

Phe

<210> 336  
 <211> 125  
 <212> PRT  
 <213> Homo sapiens

<400> 336  
 Met Ser Asn Thr Asn Gly Ser Ala Ile Thr Glu Phe Ile Leu Leu Gly  
 1 5 10 15  
 Leu Thr Asp Cys Pro Glu Leu Gln Ser Leu Leu Phe Val Leu Phe Leu  
 20 25 30  
 Val Val Tyr Leu Val Thr Leu Leu Gly Asn Leu Gly Met Ile Met Leu  
 35 40 45  
 Met Arg Leu Asp Ser Arg Leu His Thr Pro Met Tyr Phe Phe Leu Thr  
 50 55 60  
 Asn Leu Ala Phe Val Asp Leu Cys Tyr Thr Ser Asn Ala Thr Pro Gln  
 65 70 75 80  
 Met Ser Thr Asn Ile Val Ser Glu Lys Thr Ile Ser Phe Ala Gly Cys  
 85 90 95  
 Phe Thr Gln Cys Tyr Ile Phe Ile Ala Leu Leu Leu Thr Glu Phe Tyr

190

100 105 110  
 Met Leu Ala Ala Met Ala Tyr Asp Arg Tyr Val Ala Ile  
 115 120 125  
  
 <210> 337  
 <211> 132  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 337  
 Met Arg Leu Leu Val Leu Ser Ser Leu Leu Cys Ile Leu Leu Leu Cys  
 1 5 10 15  
 Phe Ser Ile Phe Ser Thr Glu Gly Lys Arg Arg Pro Ala Lys Ala Trp  
 20 25 30  
 Ser Gly Arg Arg Thr Arg Leu Cys Cys His Arg Val Pro Ser Pro Asn  
 35 40 45  
 Ser Thr Asn Leu Lys Ala Phe Thr Ala Val Ser Cys Asn Val Gly Gly  
 50 55 60  
 Leu His Leu Gly Leu Gln Gly Pro Trp Glu Ser Ser Arg Thr Pro Arg  
 65 70 75 80  
 Pro Cys Leu Asn Cys Ala Ile Asn Phe Gln Ser Tyr His Glu Pro Thr  
 85 90 95  
 Ser Pro His Arg Ala Ser Val Ala Thr Met Trp Ala Ser Pro Val Gln  
 100 105 110  
 Thr Thr Glu His Ser Thr Met Thr Gly His Ser Tyr Lys Ser Arg Asp  
 115 120 125  
 His Gln Ser Cys  
 130

<210> 338  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<400> 338  
 Met Arg Leu Leu Val Leu Ser Ser Leu Leu Cys Ile Leu Leu Leu Cys  
 1 5 10 15  
 Phe Ser Ile Phe Ser Thr Glu Gly Lys Arg Arg Pro Ala Lys Ala Trp  
 20 25 30  
 Ser Gly Arg Arg Thr Arg Leu Cys Cys His Arg Val Pro Ser Pro Asn  
 35 40 45  
 Ser Thr Asn Leu Lys Gly His His Val Arg Leu Cys Lys Pro Cys Lys  
 50 55 60  
 Leu Glu Pro Glu Pro Arg Leu Trp Val Val Pro Gly Ala Leu Pro Gln  
 65 70 75 80  
 Val

<210> 339  
 <211> 173  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (128)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (153)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (160)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (166)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 339  
 Met Ser Gly Leu Ser Arg Pro Leu Leu Leu Ala Val Gly Cys Leu Ala  
   1                  5                  10                  15  
 Ala Leu Cys Val Ile Thr Ala Ala Gly Asn Thr Thr Leu Ala Pro Asn  
                   20                  25                  30  
 Val Thr Thr Ala Ser Ser Pro Pro Pro Thr Thr Thr Thr Val Pro Val  
                   35                  40                  45  
 Ser Pro Thr Thr Leu Ser Pro Leu Pro Val Thr Thr Pro Ala Pro Asp  
   50                  55                  60  
 Ile Cys Gly Ser Arg Asn Ser Cys Val Ser Cys Val Asp Gly Asn Ala  
   65                  70                  75                  80  
 Thr Cys Phe Trp Ile Glu Cys Lys Gly Lys Ser Tyr Cys Ser Asp Asn  
                   85                  90                  95  
 Ser Thr Ala Gly Asp Cys Lys Val Val Asn Thr Thr Gly Phe Cys Ser  
                   100                  105                  110  
 Ala Lys Thr Thr Thr Leu Pro Ser Thr Thr Thr Thr Ser Thr Thr Xaa  
                   115                  120                  125  
 Thr Thr Ser Gly Thr Thr Asn Thr Thr Leu Ser Pro Thr Ile Gln Pro  
   130                  135                  140  
 Thr Arg Lys Ser Thr Phe Asp Ala Xaa Gln Phe His Trp Arg Asn Xaa  
  145                  150                  155                  160  
 Pro Cys Leu Gly Val Xaa Ala Val Ile Phe Phe Leu Tyr  
                   165                  170

<210> 340  
 <211> 91  
 <212> PRT

192

&lt;213&gt; Homo sapiens

&lt;400&gt; 340

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Met Ser Arg Cys Thr Trp Pro Ser Phe Ser Phe Phe Leu Ser Ser Phe
 1              5              10              15
Leu Ser Phe Phe Arg Trp Ser Leu Ala Leu Ser Ala Arg Leu Glu Gly
              20              25              30
Ser Gly Val Ile Leu Ala His Cys Asn Leu Arg Leu Pro Gly Ser Ser
      35              40              45
Asp Ser Pro Ala Ser Ala Ser Gln Ser Ala Gly Ile Thr Gly Met Ser
      50              55              60
Arg Cys Ala Asp Val His Leu Val Ser Ile Ile Thr Lys Ala His Leu
      65              70              75              80
Val Ser Trp Pro Leu Gln Met Asn Ile Leu Pro
              85              90

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&lt;210&gt; 341

&lt;211&gt; 139

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (23)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 341

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Pro Pro Arg Pro Gly Cys Pro Val Pro Gln Trp Gly Cys Ser Ser Ala
 1              5              10              15
Trp Pro Cys Pro Ser Gln Xaa His His His Pro Ala Asn Asp Cys Gln
      20              25              30
Thr Val Gly Arg His Ser Pro Leu Asp Leu Asn Leu Lys Ser Pro Ser
      35              40              45
Leu Pro Trp Leu Asp Pro Gly Asp Pro Phe Ala Leu Pro Ser Ala Pro
      50              55              60
Ser Pro Thr Asp Leu Leu Cys Asp Leu Arg Pro Val Cys Arg Pro Leu
      65              70              75              80
Trp Ala Ser Val Phe Pro Ala Met Lys Thr Ala Ile Ser Gln Ser Cys
      85              90              95
Val Lys Gln Lys Arg Lys Ala Gly Gly Arg Pro Trp Ala Asn Gly Arg
      100              105              110
Ala Leu Val Ile Ile Asn Ile Val Ala Ala Val Val Leu Leu Leu Leu
      115              120              125
Ile Asn Ile His Ile Ile Tyr Phe Ile Leu Thr
      130              135

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&lt;210&gt; 342

&lt;211&gt; 86

&lt;212&gt; PRT



193

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (34)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (63)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (71)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (82)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 342

Met	Val	Phe	Pro	Leu	Leu	Cys	Val	Phe	Val	Leu	Ile	Ser	Ser	Ser	Leu
1				5					10					15	

Ala	Gly	Glu	Glu	Ala	Ala	Gly	Leu	Arg	Val	Gln	Lys	Leu	Trp	Pro	Ala
		20				25						30			

Val	Xaa	Leu	Ser	His	Leu	Pro	Val	Cys	Trp	Phe	His	Cys	Ser	Gly	Ile
	35				40						45				

Trp	Ser	Glu	Val	Ile	Glu	Leu	Lys	Val	Gly	Trp	Glu	Gly	His	Xaa	Leu
	50				55					60					

Pro	Trp	Gln	Ala	His	Val	Xaa	Glu	Phe	Lys	Val	Val	Glu	His	Leu	Ile
65				70					75					80	

Ser	Xaa	Met	Gly	Ala	Gly
			85		

&lt;210&gt; 343

&lt;211&gt; 118

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 343

Met	His	Cys	His	Cys	Arg	Val	Trp	Gly	Phe	Arg	Trp	Phe	Leu	Gly	Asp
1			5					10					15		

Trp	Glu	Leu	Leu	Val	Cys	Met	Cys	Trp	Val	His	Ala	Ser	Gly	Ser	Gln
	20					25						30			

Leu	Pro	Gln	Ala	Arg	Thr	Gly	Asn	Pro	Phe	Pro	Ser	Lys	Ala	Ile	Gly
	35				40						45				

Gly	Ala	Ser	Leu	Glu	Ser	Phe	Ala	Lys	Ser	Pro	Arg	Gln	Asn	Pro	Arg
50				55					60						

Val	Gln	Asp	His	Phe	His	Gly	Ala	His	Val	Phe	Leu	Phe	Cys	Arg	Asn
65			70					75						80	

Phe	Phe	Leu	Thr	Ser	Thr	His	His	Asn	Ser	Glu	Gly	His	Val	Ser	Ser
			85					90						95	

Phe Leu Asp His Tyr Ser Glu Val Leu Gln Leu Tyr Ser Ser Gln Ser  
 100 105 110

Gly Leu Gly Leu Leu Gly  
 115

<210> 344

<211> 365

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (189)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (253)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (365)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 344

Met Phe Gly Thr Leu Leu Leu Tyr Cys Phe Phe Leu Ala Thr Val Pro  
 1 5 10 15

Ala Leu Ala Glu Thr Gly Gly Glu Arg Gln Leu Ser Pro Glu Lys Ser  
 20 25 30

Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu Pro Ala Arg  
 35 40 45

Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn Lys Phe Thr Ser  
 50 55 60

Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val Ser Ala Pro Glu Glu  
 65 70 75 80

Gln Phe Thr Arg Val Gly Val Gln Val Leu Asp Arg Lys Asp Gly Ser  
 85 90 95

Phe Ile Val Arg Tyr Arg Met Tyr Ala Ser Tyr Lys Asn Leu Lys Val  
 100 105 110

Glu Val Lys Phe Gln Gly Gln His Val Ala Lys Ser Pro Tyr Ile Leu  
 115 120 125

Lys Gly Pro Val Tyr His Glu Asn Cys Asp Cys Pro Leu Gln Asp Ser  
 130 135 140

Ala Ala Trp Leu Arg Glu Met Asn Cys Pro Glu Thr Ile Ala Gln Ile  
 145 150 155 160

Gln Arg Asp Leu Ala His Phe Pro Ala Val Asp Pro Glu Lys Ile Ala  
 165 170 175

Val Glu Ile Pro Lys Arg Phe Gly Gln Arg Gln Ser Xaa Cys His Tyr  
 180 185 190

195

Thr Leu Lys Asp Asn Lys Val Tyr Ile Lys Thr His Gly Glu His Val  
 195 200 205  
 Gly Phe Arg Ile Phe Met Asp Ala Ile Leu Leu Ser Leu Thr Arg Lys  
 210 215 220  
 Val Lys Met Pro Asp Val Glu Leu Phe Val Asn Leu Gly Asp Trp Pro  
 225 230 235 240  
 Leu Glu Lys Lys Lys Ser Asn Ser Asn Ile His Pro Xaa Phe Ser Trp  
 245 250 255  
 Cys Gly Ser Thr Asp Ser Lys Asp Ile Val Met Pro Thr Tyr Asp Leu  
 260 265 270  
 Thr Asp Ser Val Leu Glu Thr Met Gly Arg Val Ser Leu Asp Met Met  
 275 280 285  
 Ser Val Gln Ala Asn Thr Gly Pro Pro Trp Glu Ser Lys Asn Ser Thr  
 290 295 300  
 Ala Val Trp Arg Gly Arg Asp Ser Arg Lys Glu Arg Leu Glu Leu Val  
 305 310 315 320  
 Lys Leu Ser Arg Lys His Pro Glu Leu Ile Asp Ala Ala Phe Thr Asn  
 325 330 335  
 Phe Phe Phe Phe Lys His Asp Glu Asn Leu Tyr Gly Pro Ile Val Asn  
 340 345 350  
 Ile Phe His Phe Leu Ile Ser Ser Ser Ile Ser Ile Xaa  
 355 360 365

&lt;210&gt; 345

&lt;211&gt; 62

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 345

Met Thr Xaa Gln Leu Leu Phe Asn Ser Phe Leu Leu Ser Ser Val Ser  
 1 5 10 15  
 Gln Ile Arg Asp Gln Ile Ala Met Arg Glu Ser Val Trp Ser Gly Ser  
 20 25 30  
 Ile Ser Arg Gln Lys Glu Leu Val Thr Leu Trp Ile Ile Cys Leu Trp  
 35 40 45  
 Phe Arg His Leu Pro Leu Val Leu Ala Val Gly Asp Gly Trp  
 50 55 60

&lt;210&gt; 346

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

196

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 346

Cys Pro Ala Leu Phe Asn Ile Xaa Phe Glu Asn Ser Ile Leu Tyr Cys  
 1 5 10 15

Gln Ile

&lt;210&gt; 347

&lt;211&gt; 306

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 347

Met Gly His Arg Thr Leu Val Leu Pro Trp Val Leu Leu Thr Leu Cys  
 1 5 10 15

Val Thr Ala Gly Thr Pro Glu Val Trp Val Gln Val Arg Met Glu Ala  
 20 25 30

Thr Glu Leu Ser Ser Phe Thr Ile Arg Cys Gly Phe Leu Gly Ser Gly  
 35 40 45

Ser Ile Ser Leu Val Thr Val Ser Trp Gly Gly Pro Asp Gly Ala Gly  
 50 55 60

Gly Thr Thr Leu Ala Val Leu His Pro Glu Arg Gly Ile Arg Gln Trp  
 65 70 75 80

Ala Pro Ala Arg Gln Ala Arg Trp Glu Thr Gln Ser Ser Ile Ser Leu  
 85 90 95

Ile Leu Glu Gly Ser Gly Ala Ser Ser Pro Cys Ala Asn Thr Thr Phe  
 100 105 110

Cys Cys Lys Phe Ala Ser Phe Pro Glu Gly Ser Trp Glu Ala Cys Gly  
 115 120 125

Ser Leu Pro Pro Ser Ser Asp Pro Gly Leu Ser Ala Pro Pro Thr Pro  
 130 135 140

Ala Pro Ile Leu Arg Ala Asp Leu Ala Gly Ile Leu Gly Val Ser Gly  
 145 150 155 160

Val Leu Leu Phe Gly Cys Val Tyr Leu Leu His Leu Leu Arg Arg His  
 165 170 175

Lys His Arg Pro Ala Pro Arg Leu Gln Pro Ser Arg Thr Ser Pro Gln  
 180 185 190

Ala Pro Arg Ala Arg Ala Trp Ala Pro Ser Gln Ala Ser Gln Ala Ala  
 195 200 205

Leu His Val Pro Tyr Ala Thr Ile Asn Thr Ser Cys Arg Pro Ala Thr  
 210 215 220

Leu Asp Thr Ala His Pro His Gly Gly Pro Ser Trp Trp Ala Ser Leu  
 225 230 235 240

Pro Thr His Ala Ala His Arg Pro Gln Gly Pro Ala Ala Trp Ala Ser

197

245								250				255			
Thr	Pro	Ile	Pro 260	Ala	Arg	Gly	Ser	Phe 265	Val	Ser	Val	Glu	Asn 270	Gly	Leu
Tyr	Ala	Gln 275	Ala	Gly	Glu	Arg	Pro 280	Pro	His	Thr	Gly	Pro 285	Gly	Leu	Thr
Leu	Phe 290	Pro	Asp	Pro	Arg	Gly 295	Pro	Arg	Ala	Met	Glu 300	Gly	Pro	Leu	Gly
Val 305	Arg														

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<210> 348
<211> 106
<212> PRT
<213> Homo sapiens
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<220>  
<221> SITE  
<222> (94)  
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (102)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (106)
<223> Xaa equals any of the naturally occurring L-amino acids

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<400> 348
Met Gly Trp Ser Arg Gly Glu Gly Gln Gln Gly Trp Leu Ala Ala Ala
  1          5          10
Leu Cys Gly Trp Thr Arg Leu Gly Lys Ala Glu Gly Ser Glu Gly Trp
      20          25          30
Ala Thr Leu Glu Gly Cys Gln Val Pro Ser Leu Leu Gln Gly Asn Glu
      35          40          45
Gly Gly Ala Ala Leu Asn Arg His Met Pro Lys Gln Gly Ile Asp Ala
  50          55          60
Trp Ile Lys Leu Ala Thr Thr Arg Arg Ser Leu Phe Gly Ile Phe Gln
  65          70          75          80
Ile Leu Arg His Pro Ser Cys Asp Asp Gly Val Glu Arg Xaa Thr Gly
      85          90          95
Pro Leu Glu Phe Cys Xaa Leu His Arg Xaa
      100          105

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<210> 349
<211> 137
<212> PRT
<213> Homo sapiens
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<400> 349

198

Ala Leu Met Ser Arg Gln Arg Gly Pro Gly Glu Asn Pro Ala Pro Ser  
 1 5 10 15  
 Val Ile Pro Leu His Phe Leu Pro Ser Phe Leu Leu Cys Leu Ala Lys  
 20 25 30  
 Glu Gly Ser Ser Leu Gly Cys Pro Tyr Asn Ala Pro Gly Pro Arg Leu  
 35 40 45  
 Ser Asn Lys Lys Pro Glu Pro Cys Gly Pro Val Ala Arg Ala Ser Ser  
 50 55 60  
 Gly Arg Leu Pro Leu Leu Cys Leu Gly Pro Leu Ser Pro Ala Ser Arg  
 65 70 75 80  
 Ala Arg Val Arg Leu Gln Ala Ser Gly His Cys Pro Gly Cys Asp Gly  
 85 90 95  
 Thr Lys Ala Gly Gly Ala Pro Gly Thr Thr Gln Leu Gly Phe Pro Pro  
 100 105 110  
 Gly Phe Pro Ala Gly Val Ser Gly Ser Phe Ser Pro Ala Leu Leu Gly  
 115 120 125  
 Val Cys Arg Asn Trp Pro Cys Ser Pro  
 130 135

&lt;210&gt; 350

&lt;211&gt; 102

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (11)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 350

Glu Thr Arg Thr Leu Gln Pro Pro Gly Pro Xaa Cys Val Cys Arg Pro  
 1 5 10 15  
 Val Ala Thr Val Arg Ala Val Met Ala Pro Arg Gln Val Glu His Gln  
 20 25 30  
 Val Pro His Ser Trp Ala Ser His Gln Ala Phe Pro Arg Gly Ser Gln  
 35 40 45  
 Gly Ala Ser Pro Gln Arg Cys Xaa Glu Ser Ala Gly Thr Gly Leu Val  
 50 55 60  
 Leu Leu Ser Pro Ser Leu His Thr Val Leu Gly Glu Asp Gly Cys Gly  
 65 70 75 80  
 Arg Cys Pro Cys Arg Glu Val Thr Val Glu Val Ala Val Ala Cys Ser  
 85 90 95  
 His Leu Trp Glu Glu Lys  
 100

199

<210> 351  
 <211> 133  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (131)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 351  
 Met Arg Leu Phe Val Ser Val Thr Val Leu Val Ile Cys Leu Ala Asp  
           1                  5                  10                  15  
 Leu Glu Glu Glu Ser Glu Ser Trp Asp Asn Ser Glu Ser Glu Glu Glu  
                   20                  25                  30  
 Glu Lys Ala Pro Val Leu Pro Glu Ser Thr Glu Gly Arg Glu Leu Thr  
           35                  40                  45  
 Gln Gly Pro Ala Glu Ser Ser Ser Leu Ser Gly Cys Gly Ser Trp Gln  
           50                  55                  60  
 Pro Arg Lys Leu Pro Val Phe Lys Ser Leu Arg His Met Arg Gln Val  
           65                  70                  75                  80  
 Gly Gly Arg Gly Thr Ala His Gln Glu Leu Arg Arg Arg Ala Asn His  
                   85                  90                  95  
 Gly Leu Ser Leu Pro Thr Arg Leu Ala Ser Gly Pro Ser Thr Phe Lys  
                   100                  105                  110  
 Thr Leu Gln Glu Val Thr Asp Ser Leu Leu Gly Gly Trp Leu Arg Ala  
           115                  120                  125  
 Gln Gly Xaa Gly Gly  
           130

<210> 352  
 <211> 136  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (96)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (98)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 352  
 Met Ile Leu Leu Ile Ile Leu Trp Ile Leu Arg Glu Ile Gln Ser Ile  
           1                  5                  10                  15  
 Tyr Ile Ile Gly Ile Phe Arg Asn Pro Phe Tyr Pro Lys Asp Val Gln  
                   20                  25                  30  
 Thr Val Thr Val Phe Phe Glu Lys Gln Thr Arg Leu Met Lys Ile Gly  
           35                  40                  45



200

Ile Val Arg Arg Ile Leu Leu Thr Leu Val Ser Pro Phe Ala Met Ile  
 50 55 60  
 Ala Phe Leu Ser Leu Asp Ser Ser Leu Gln Gly Leu His Ser Val Ser  
 65 70 75 80  
 Val Cys Ile Gly Phe Thr Arg Ala Phe Arg Met Val Trp Gln Asn Xaa  
 85 90 95  
 Glu Xaa Ala Leu Leu Glu Thr Val Ile Val Ser Thr Val His Leu Ile  
 100 105 110  
 Ser Ser Thr Asp Ile Trp Trp Asn Arg Ser Leu Asp Thr Gly Leu Arg  
 115 120 125  
 Leu Leu Leu Val Gly Ile His Thr  
 130 135

<210> 353  
 <211> 134  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (133)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 353  
 Met Ile Leu Leu Ile Ile Leu Trp Ile Leu Arg Glu Ile Gln Ser Ile  
 1 5 10 15  
 Tyr Ile Ile Gly Ile Phe Arg Asn Pro Phe Tyr Pro Lys Asp Val Gln  
 20 25 30  
 Thr Val Thr Val Phe Phe Glu Lys Gln Thr Arg Leu Xaa Lys Ile Gly  
 35 40 45  
 Ile Val Arg Arg Ile Leu Leu Thr Leu Val Ser Pro Phe Ala Met Ile  
 50 55 60  
 Ala Phe Leu Ser Leu Asp Ser Ser Leu Gln Gly Leu His Ser Val Ser  
 65 70 75 80  
 Val Cys Ile Gly Phe Thr Arg Ala Phe Arg Met Val Trp Gln Asn Thr  
 85 90 95  
 Glu Asn Ala Leu Leu Glu Thr Val Ile Val Ser Thr Val His Leu Ile  
 100 105 110  
 Ser Ser Thr Asp Ile Trp Trp Asn Arg Ser Leu Asp Thr Gly Gly Thr  
 115 120 125  
 His Phe Val Asn Xaa Val  
 130



201

&lt;210&gt; 354

&lt;211&gt; 303

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 354

Gly Arg Leu Arg Gly Ala Gly Arg Gly Val Gln Arg Ala Met Ala Ala  
 1 5 10 15  
 Leu Arg Val Leu Leu Ser Cys Ala Arg Gly Pro Leu Arg Pro Pro Val  
 20 25 30  
 Arg Cys Pro Ala Trp Arg Pro Phe Ala Ser Gly Ala Asn Phe Glu Tyr  
 35 40 45  
 Ile Ile Ala Glu Lys Arg Gly Lys Asn Asn Thr Val Gly Leu Ile Gln  
 50 55 60  
 Leu Asn Arg Pro Lys Ala Leu Asn Ala Leu Cys Asp Gly Leu Ile Asp  
 65 70 75 80  
 Glu Leu Asn Gln Ala Leu Lys Ile Phe Glu Glu Asp Pro Ala Val Gly  
 85 90 95  
 Ala Ile Val Leu Thr Gly Gly Asp Lys Ala Phe Ala Ala Gly Ala Asp  
 100 105 110  
 Ile Lys Glu Met Gln Asn Leu Ser Phe Gln Asp Cys Tyr Ser Ser Lys  
 115 120 125  
 Phe Leu Lys His Trp Asp His Leu Thr Gln Val Lys Lys Pro Val Ile  
 130 135 140  
 Ala Ala Val Asn Gly Tyr Ala Phe Gly Gly Gly Cys Glu Leu Ala Met  
 145 150 155 160  
 Met Cys Asp Ile Ile Tyr Ala Gly Glu Lys Ala Gln Phe Ala Gln Pro  
 165 170 175  
 Glu Ile Leu Ile Gly Thr Ile Pro Gly Ala Gly Gly Thr Gln Arg Leu  
 180 185 190  
 Thr Arg Ala Val Gly Lys Ser Leu Ala Met Glu Met Val Leu Thr Gly  
 195 200 205  
 Asp Arg Ile Ser Ala Gln Asp Ala Lys Gln Ala Gly Leu Val Ser Lys  
 210 215 220  
 Ile Cys Pro Val Glu Thr Leu Val Glu Glu Ala Ile Gln Cys Ala Glu  
 225 230 235 240  
 Lys Ile Ala Ser Asn Ser Lys Ile Val Val Ala Met Ala Lys Glu Ser  
 245 250 255  
 Val Asn Ala Ala Phe Glu Met Thr Leu Thr Glu Gly Ser Lys Leu Glu  
 260 265 270  
 Lys Lys Leu Phe Tyr Ser Thr Phe Ala Thr Asp Asp Arg Lys Glu Gly  
 275 280 285  
 Met Thr Ala Phe Val Glu Lys Arg Lys Ala Asn Phe Lys Asp Gln  
 290 295 300

&lt;210&gt; 355

202

<211> 118  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 355  
 Met Glu Met Ala Ser Ser Ala Gly Ser Trp Leu Ser Gly Cys Leu Ile  
   1                  5                  10                  15  
 Pro Leu Val Phe Leu Arg Leu Ser Val His Val Ser Gly His Ala Gly  
                   20                  25                  30  
 Asp Ala Gly Lys Phe His Val Ala Leu Leu Gly Gly Thr Ala Glu Leu  
                   35                  40                  45  
 Leu Cys Pro Leu Ser Leu Trp Pro Gly Thr Val Pro Lys Xaa Val Arg  
   50                  55                  60  
 Trp Leu Arg Ser Pro Phe Pro Gln Arg Ser Gln Ala Val His Ile Phe  
   65                  70                  75                  80  
 Arg Asp Gly Lys Asp Gln Asp Glu Asp Leu Met Pro Glu Tyr Lys Gly  
                   85                  90                  95  
 Arg Thr Val Leu Val Arg Asp Ala Gln Glu Gly Ser Val Thr Leu Gln  
                   100                  105                  110  
 Ile Leu Asp Val Arg Leu  
                   115

<210> 356  
 <211> 93  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (75)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 356  
 Met Ser His Cys Cys Ser Leu Arg Val Asp Phe Ser Val Pro Leu Cys  
   1                  5                  10                  15  
 Met Leu Leu Ser Pro Leu Leu Gly Met Ser Phe Ser Ala Cys Gln Thr  
                   20                  25                  30  
 Pro Ser Lys Ser Ser Ser Asp Val Thr Phe Ser Leu Ser Thr Pro Asp  
                   35                  40                  45  
 Pro Thr Pro Gln Ile Asp Leu Val Gln Pro Ser Ser Gly Phe Pro Gln  
   50                  55                  60  
 His Ser Val Gln Phe Glu Arg Ser Phe Ile Xaa Val Ile Ile Thr Phe  
   65                  70                  75                  80  
 Phe Lys Asn Asn Phe Ile Phe Ile Asn Leu Ile Arg Leu  
                   85                  90

203

<210> 357  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<400> 357  
 Met Leu His Ser Leu Ala Leu Ala Glu Phe Cys Arg Asp Trp Gln His  
 1 5 10 15  
 Cys Val Pro Ala Cys Ser Pro Thr Val Ala Val Leu Phe Pro Arg Val  
 20 25 30  
 Gln Arg Arg Phe Phe Leu Cys Ala Leu Trp Leu Leu Arg Ala His Gly  
 35 40 45  
 Gly Gly Leu Gly Ser Ala Ile Gln Asp Cys Leu Phe Tyr Pro Leu His  
 50 55 60  
 Cys Leu Phe Gln Gln Tyr Glu Gly Thr Val Ile Ala His Met Ile Phe  
 65 70 75 80  
 Gly Ser Tyr Glu Gly Ala Phe Cys Val Gly Gly Cys Gln Ile Trp Cys  
 85 90 95  
 Ser Cys Arg Glu Asp Asn Arg Trp Arg Leu Leu Phe Gly His Ile Ala  
 100 105 110  
 Leu Pro Pro Ile Pro Ala Cys Phe Tyr Phe  
 115 120

<210> 358  
 <211> 95  
 <212> PRT  
 <213> Homo sapiens

<400> 358  
 Met Gly Ala Ala Trp Pro Arg Arg Ala Arg Ser Trp Trp Ile Arg Thr  
 1 5 10 15  
 Ser Thr Ala Ser Ser Pro Ser Pro Ser Ser Ser Ile Thr Leu Leu Trp  
 20 25 30  
 Thr Pro Cys Met Trp Ala Glu Ser Trp Ala Cys Cys Ser Ser Pro Thr  
 35 40 45  
 Tyr Thr Arg Thr Gly Lys Cys Ser Thr Asn Arg Thr Pro Arg Trp Pro  
 50 55 60  
 Pro Ala Leu Thr Ser Met Pro Arg Thr Ser Thr Phe Gln Gln Trp Leu  
 65 70 75 80  
 Ser Ser Pro Thr Phe Trp Trp Leu Ala Cys Ala Gly Asp Pro Gly  
 85 90 95

<210> 359  
 <211> 129  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE

204

&lt;222&gt; (52)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (110)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 359

Met	Asn	Lys	Arg	Ala	Lys	Phe	Glu	Leu	Arg	Lys	Pro	Leu	Val	Leu	Trp
1				5					10					15	

Ser	Leu	Thr	Leu	Ala	Val	Phe	Ser	Ile	Phe	Gly	Ala	Leu	Arg	Thr	Gly
			20					25					30		

Ala	Tyr	Met	Val	Tyr	Ile	Leu	Met	Thr	Lys	Gly	Leu	Lys	Gln	Ser	Val
		35					40					45			

Cys	Asp	Gln	Xaa	Phe	Tyr	Asn	Gly	Pro	Val	Ser	Lys	Phe	Trp	Ala	Tyr
	50					55					60				

Ala	Phe	Val	Leu	Ser	Lys	Ala	Pro	Glu	Leu	Gly	Asp	Thr	Ile	Phe	Ile
65					70					75					80

Ile	Leu	Arg	Lys	Gln	Lys	Leu	Ile	Phe	Leu	His	Trp	Tyr	His	His	Ile
				85					90					95	

Thr	Val	Leu	Leu	Tyr	Ser	Trp	Tyr	Ser	Tyr	Lys	Asp	Met	Xaa	Cys	Arg
			100					105					110		

Gly	Gly	Trp	Phe	Met	Thr	Met	Asn	Tyr	Gly	Val	His	Ala	Val	Met	Tyr
		115					120					125			

Ser

&lt;210&gt; 360

&lt;211&gt; 84

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 360

Met	Gly	Asp	Lys	Glu	Ser	Ser	Ser	Ser	Lys	Pro	Ser	Leu	Ala	Gly	Trp
1				5					10					15	

Val	Pro	Leu	Leu	Leu	Gly	Gly	Ala	Phe	Ser	Cys	Thr	Pro	Leu	Pro	Pro
			20					25					30		

Arg	Gly	Glu	Ser	Gln	Gln	Pro	Asn	Gln	Thr	Ala	Gln	Val	Val	His	Leu
		35					40					45			

Met	Glu	Thr	Thr	Gly	Leu	Lys	His	Val	Leu	Tyr	Ser	Pro	Val	Tyr	Phe
	50					55					60				

Cys	Cys	Tyr	Phe	Glu	Ala	Trp	Lys	Phe	Leu	Phe	Gly	Gly	Ser	Trp	Gly
65					70					75					80

Tyr Ser Ser Gly

&lt;210&gt; 361

&lt;211&gt; 88

205

<212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (11)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (19)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (23)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (56)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (57)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 361  
 Thr Ser Asn Val Asn Ala Gln Asn His Gln Xaa Pro Thr His Leu Arg  
   1                  5                  10                  15  
 Val Asn Xaa Tyr Asp Val Xaa Phe Gly Val Asn Val Gly Asn Glu Thr  
                   20                  25                  30  
 Ala Met Lys Ala Pro Glu Leu Lys Asp Val Gly Lys Trp Ala Ala Val  
           35                  40                  45  
 His Cys Pro Ala Leu Gln Gly Xaa Xaa Glu Ala Cys Leu Leu Ala Ser  
   50                  55                  60  
 Gly Gly Gly Ala Arg Leu Gln Glu Gly Pro Ala Thr Cys His Leu Pro  
   65                  70                  75                  80  
 Cys Asp Gln Ala Lys Lys Trp Asn  
                   85  
  
 <210> 362  
 <211> 116  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (11)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 362  
 Met Ala Leu Asp Ile Ser Leu Phe Tyr Leu Xaa Tyr Phe Phe Phe Phe  
   1                  5                  10                  15  
 Leu Arg Trp Asn Phe Ser Leu Ile Ala Gln Ala Gly Val Gln Trp His  
           20                  25                  30

```
<210> 363
<211> 139
<212> PRT
<213> Homo sapiens
```

<400> 363															
Met	Leu	Ala	Met	Leu	Leu	Cys	Met	Leu	Val	Ser	Val	Phe	Ile	Leu	Gly
1				5					10					15	
Val	Pro	Tyr	Arg	Gly	Ser	Leu	Leu	Ile	Leu	Phe	Phe	Ile	Ser	Ser	Leu
			20					25					30		
Phe	Leu	Leu	Ser	Thr	Leu	Gly	Met	Gly	Leu	Leu	Ile	Ser	Thr	Ile	Thr
		35					40					45			
Arg	Asn	Gln	Phe	Asn	Ala	Ala	Gln	Val	Ala	Leu	Asn	Ala	Ala	Phe	Leu
	50					55					60				
Pro	Ser	Ile	Met	Leu	Ser	Gly	Phe	Ile	Phe	Gln	Ile	Asp	Ser	Met	Pro
65					70					75					80
Ala	Val	Ile	Arg	Ala	Val	Thr	Tyr	Ile	Ile	Pro	Ala	Arg	Tyr	Phe	Val
				85					90					95	
Ser	Thr	Leu	Gln	Ser	Leu	Phe	Leu	Ala	Gly	Asn	Ile	Pro	Val	Val	Leu
			100					105					110		
Val	Val	Asn	Val	Leu	Phe	Leu	Ile	Ala	Ser	Ala	Val	Met	Phe	Ile	Gly
		115					120					125			
Leu	Thr	Trp	Leu	Lys	Thr	Lys	Arg	Arg	Leu	Asp					
	130					135									

```
<210> 364
<211> 82
<212> PRT
<213> Homo sapiens
```

<400> 364  
Met Gly Trp Gln Leu Arg Ala Leu Ser Ala Val Gly Leu Trp Phe Thr  
1 5 10 15  
Ala Gly Asp Ser His Leu Ser Val Gln Val Cys Gly Gly Gly Pro Ala  
20 25 30

Leu Thr Leu Trp His Leu Arg Ser Ser Thr Pro Thr Thr Ile Phe Pro  
35 40 45

Ile Arg Ala Pro Gln Lys His Val Thr Phe Tyr Gln Asp Leu Val Arg  
50 55 60

Pro Cys Val Ser Leu Leu Pro Pro Pro Leu Thr Leu Pro Phe Ser Pro  
65 70 75 80

Asp Pro

```
<210> 365
<211> 59
<212> PRT
<213> Homo sapiens
```

```

<400> 365
Met Leu Cys His Ala Trp Leu Leu Leu Met Tyr Leu Phe Leu Glu Met
 1          5          10          15
Arg Ser His Cys Val Ala Gln Thr Gly Leu Glu Leu Leu Ala Ser Ser
          20          25          30
His Pro Pro Phe Ser Ala Ser Thr Val Ala Gly Ile Ser Gly Thr Cys
          35          40          45
..
His Cys Ala Leu Leu Ile Pro Phe Lys Ile Arg
 50          55

```

```
<210> 366
<211> 101
<212> PRT
<213> Homo sapiens
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```
<220>
<221> SITE
<222> (8)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```
<220>
<221> SITE
<222> (100)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```

<400> 366
Met Asp His Met Ala Ser Asp Xaa Leu Glu Arg Leu Leu Val Ala Met
 1          5          10          15
Val Phe Pro Cys Ala Gln Glu Val Glu Asn Glu Ile Gly Phe Gly Glu
          20          25          30
His Leu Ala Leu Ala Arg Ser Gln Pro Pro Asp Phe Lys Ala Thr Phe
          35          40          45
Leu Lys Pro Lys Val Val Val Gly Gln Val Trp Trp Leu Met Cys Val
          50          55          60
Ile Pro Ala Leu Trp Glu Thr Glu Arg Val Asp His Leu Arg Ser Arg
 65          70          75          80

```

208

Ala Gln Asp Gln Pro Ala Gln Cys Gly Lys Thr Pro Ser Leu Leu Lys  
                             85                            90                            95

Ile Gln Thr Xaa Asn  
                             100

<210> 367  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 367  
 Met Ile His Leu Phe Leu Leu Pro Cys Pro Asn Cys Val Phe Leu Leu  
     1                            5                            10                            15  
 Leu His Leu Phe Phe Gln Gln Cys Ala Ala Ser Trp Thr Thr Ser  
                             20                            25                            30

<210> 368  
 <211> 118  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 368  
 Ala Asn Thr Ser Thr Arg Ala Ala Leu Tyr Cys Leu Phe Leu Ser Phe  
     1                            5                            10                            15  
 Ile Met Phe Ala Ser Val Leu Gln Ile Asn Pro Arg Ser Trp Leu Met  
                             20                            25                            30  
 Lys Xaa Val Ile Thr Val Leu Ala Ala Cys Leu Glu Ser Glu Asn Gln  
                             35                            40                            45  
 Asn Ala Gln Arg Ile Gly Ala Ala Ala Leu Trp Ala Leu Ile Tyr Asn  
                             50                            55                            60  
 Tyr Gln Lys Ala Lys Thr Ala Leu Lys Ser Pro Ser Val Lys Arg Arg  
     65                            70                            75                            80  
 Val Asp Glu Ala Tyr Ser Leu Ala Lys Lys Thr Phe Pro Asn Ser Glu  
                             85                            90                            95  
 Ala Asn Pro Leu Asn Ala Tyr Tyr Leu Lys Cys Leu Glu Asn Leu Val  
                             100                            105                            110  
 Gln Leu Leu Asn Ser Ser  
                             115

<210> 369  
 <211> 87  
 <212> PRT  
 <213> Homo sapiens

<400> 369  
 Met Thr Leu Leu Leu Thr Leu Glu Val Asp Pro Gly Thr Gln Gln Arg



209

1		5		10		15									
Ala	Gly	Val	Gly	Ser	Gln	Gly	Gln	Ala	Val	Leu	Pro	Gly	Leu	Thr	Cys
		20						25					30		
Phe	Leu	Leu	Thr	Phe	Leu	Leu	Ala	Ala	Ser	Val	Tyr	Ile	Thr	Gln	Ser
		35					40					45			
Ala	Trp	Asp	Asn	Val	Glu	Val	Ala	Glu	Val	Thr	Gly	Tyr	Phe	Met	Phe
	50					55					60				
Leu	His	Gly	Ile	Phe	Leu	Phe	Leu	Ile	Gly	Arg	Arg	Arg	Gln	Lys	Leu
65					70					75					80
Glu	Glu	Met	Gly	Leu	Leu	Ser									
				85											

<210> 370  
 <211> 73  
 <212> PRT  
 <213> Homo sapiens

<400> 370  
 Met Tyr Pro Val Tyr Thr Thr Ser Asp Phe Cys Ser Gly Thr Phe Val  
 1 5 10 15  
 Leu Ile Phe Ala Trp Leu Thr Leu Ser Glu Leu Val Arg Val Leu His  
 20 25 30  
 Arg Lys Ile Ile Asn Trp Phe Phe Ile Phe Leu Arg Arg Phe Tyr Tyr  
 35 40 45  
 Gly Glu Leu Ala Tyr Ala Asn Met Glu Thr Thr Met Cys His Leu Gln  
 50 55 60  
 Ala Gly Asp Pro Arg Gln Leu Val Val  
 65 70

<210> 371  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<400> 371  
 Met Tyr Ser Pro Ser Leu Tyr Leu Leu Pro Ser Leu Pro Ser Leu Leu  
 1 5 10 15  
 Gln Leu Ser Leu Ser Arg Ser Pro Arg Phe Asn Lys Gly Leu Gln Arg  
 20 25 30  
 Ala Met Glu Lys Thr Met Lys Gly Ser Thr Ile Lys Ile Leu Leu Tyr  
 35 40 45  
 Phe Phe His His Ile Tyr Ala Ser Leu His Thr Phe Ile Pro Leu Pro  
 50 55 60  
 Asn Pro Ser Ile Phe Leu Cys Ile Ser Lys Tyr Ile Ala Asp Ile Ser  
 65 70 75 80

Thr

210

<210> 372  
 <211> 61  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (6)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 372  
 Met Ser Lys Lys Ser Xaa Ser Tyr Lys Ile Arg Tyr Phe Ser Gln Ala  
 1 5 10 15  
 Trp Gln Leu Met Pro Val Ile Leu Val Leu Trp Glu Ala Glu Ala Gly  
 20 25 30  
 Gly Ser Leu Glu Ala Arg Gln Asp His Ile Xaa Arg Leu Cys Leu Cys  
 35 40 45  
 Lys Lys Lys Lys Arg Ala Ala Pro Leu Phe Phe Phe Phe  
 50 55 60  
  
 <210> 373  
 <211> 83  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 373  
 Met Leu Cys Ser Ser Phe Leu Pro Leu Ser Thr Ala Ala Ile Trp Ala  
 1 5 10 15  
 Ala Leu Phe Ser Gly Met Gly Ala Val Arg His Ser Pro Ser Glu Gly  
 20 25 30  
 Lys Arg Ser Leu Lys Ser Ser Arg Cys Leu His Phe Trp Pro Leu Pro  
 35 40 45  
 Thr Gly Cys Ser Ser Pro Pro Pro Pro Cys Asn Val Thr Thr Lys Asn  
 50 55 60  
 Val Ser Arg Cys Cys Gln Lys Ser Ser Arg Asp Gly Arg Val Arg Leu  
 65 70 75 80  
 Pro Pro Arg  
  
 <210> 374  
 <211> 84  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 374  
 Met Gly Leu Arg Leu Pro Pro Pro Leu Cys Trp Phe Leu Cys Leu Thr  
 1 5 10 15

211

Ser Thr Gly Gln Val Pro Met Ala Gln Ala Arg Ala Gly Val Gln Gly  
                   20                  25                  30  
 Pro Met Asp Gly Arg Met Pro Ser Asn Gly Cys Leu Pro Val Ser Pro  
                   35                  40                  45  
 Arg Thr Pro Tyr Gly Met Pro Tyr Leu Gly Ala Leu Trp Pro Cys Trp  
                   50                  55                  60  
 Pro Cys Ser Trp Gln Gly Arg Ser Thr Ser Arg His Pro Cys Gln Gln  
                   65                  70                  75                  80  
 Asp Leu Ser Gly

<210> 375  
 <211> 143  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (97)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (99)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (104)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (107)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 375  
 Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu  
           1                  5                  10                  15  
 Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys  
                   20                  25                  30  
 Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp  
                   35                  40                  45  
 Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala  
                   50                  55                  60  
 Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu  
                   65                  70                  75                  80  
 Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Pro Pro Gly Met Pro  
                   85                  90                  95  
 Xaa Val Xaa Gly Pro Met Gly Xaa Pro Gly Xaa Pro Glu Ile Pro Val  
                   100                  105                  110  
 Ser Val His Gly His Ser Ala Asp Pro Pro Ala Pro Cys Thr Gln Gln

212

115	120	125
Pro Asp Gln Ile Gln Arg Gly	Pro His Gln Pro Ala	Gly Arg Leu
130	135	140

<210> 376  
 <211> 245  
 <212> PRT  
 <213> Homo sapiens

<400> 376  
 Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu  
 1 5 10 15  
 Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys  
 20 25 30  
 Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp  
 35 40 45  
 Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala  
 50 55 60  
 Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu  
 65 70 75 80  
 Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Pro Pro Gly Met Pro  
 85 90 95  
 Gly Val Pro Gly Pro Met Gly Ile Pro Gly Glu Pro Gly Glu Glu Gly  
 100 105 110  
 Arg Tyr Lys Gln Lys Phe Gln Ser Val Phe Thr Val Thr Arg Gln Thr  
 115 120 125  
 His Gln Pro Pro Ala Pro Asn Ser Leu Ile Arg Phe Asn Ala Val Leu  
 130 135 140  
 Thr Asn Pro Gln Gly Asp Tyr Asp Thr Ser Thr Gly Lys Phe Thr Cys  
 145 150 155 160  
 Lys Val Pro Gly Leu Tyr Tyr Phe Val Tyr His Ala Ser His Thr Ala  
 165 170 175  
 Asn Leu Cys Val Leu Leu Tyr Arg Ser Gly Val Lys Val Val Thr Phe  
 180 185 190  
 Cys Gly His Thr Ser Lys Thr Asn Gln Val Asn Ser Gly Gly Val Leu  
 195 200 205  
 Leu Arg Leu Gln Val Gly Glu Glu Val Trp Leu Ala Val Asn Asp Tyr  
 210 215 220  
 Tyr Asp Met Val Gly Ile Gln Gly Ser Asp Ser Val Phe Ser Gly Phe  
 225 230 235 240  
 Leu Leu Phe Pro Asp  
 245

<210> 377  
 <211> 83  
 <212> PRT

213

&lt;213&gt; Homo sapiens

&lt;400&gt; 377

```

Met Cys Ala Met Ala Pro Leu Trp Ser Pro Leu Cys Pro Ser Ile Cys
 1           5           10           15
Met Cys Ser Val Ser Leu Ala Cys Val Arg Val Arg Val Ser Ala Tyr
           20           25           30
Ala Ser Thr His Trp Ala Leu Gly Cys Ser Gln Gly Lys Phe Asp Leu
           35           40           45
Glu Arg Leu Ser Ser Pro Trp Asn Gln Asp Phe Leu Ser Pro Pro His
           50           55           60
Pro Gly Pro Val Pro Pro Trp Leu Ser Gly Tyr Trp Gly Met Glu Thr
           65           70           75           80
Leu Gly Glu

```

&lt;210&gt; 378

&lt;211&gt; 91

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 378

```

Met Arg Pro Gln Glu Leu Pro Arg Leu Ala Phe Pro Leu Leu Leu Leu
 1           5           10           15
Leu Leu Leu Leu Leu Pro Pro Pro Pro Cys Pro Ala His Ser Ala Thr
           20           25           30
Arg Phe Asp Pro Thr Trp Glu Ser Leu Asp Ala Arg Gln Leu Pro Ala
           35           40           45
Trp Phe Asp Gln Ala Lys Phe Gly Ile Phe Ile His Trp Gly Val Phe
           50           55           60
Ser Val Pro Ser Phe Gly Ser Glu Trp Phe Trp Leu Tyr Leu Val Gly
           65           70           75           80
Val Arg Ile Phe Val Glu Leu Glu Cys His Arg
           85           90

```

&lt;210&gt; 379

&lt;211&gt; 336

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 379

```

Met Leu Glu Thr Gly Leu Phe Phe Leu Leu Ser Trp Ser Ala Phe Leu
 1           5           10           15
Ser Ala Glu Ala Ala Gly Leu Thr Gly Ile Val Ala Val Leu Phe Cys
           20           25           30
Gly Val Thr Gln Ala His Tyr Thr Tyr Asn Asn Leu Ser Ser Asp Ser
           35           40           45
Lys Ile Arg Thr Lys Gln Leu Phe Glu Phe Met Asn Phe Leu Ala Glu
           50           55           60

```

214

Asn	Val	Ile	Phe	Cys	Tyr	Met	Gly	Leu	Ala	Leu	Phe	Thr	Phe	Gln	Asn
65					70					75					80
His	Ile	Phe	Asn	Ala	Leu	Phe	Ile	Leu	Gly	Ala	Phe	Leu	Ala	Ile	Phe
				85					90					95	
Val	Ala	Arg	Ala	Cys	Asn	Ile	Tyr	Pro	Leu	Ser	Phe	Leu	Leu	Asn	Leu
			100					105					110		
Gly	Arg	Lys	Gln	Lys	Ile	Pro	Trp	Asn	Phe	Gln	His	Met	Met	Met	Phe
		115					120					125			
Ser	Gly	Leu	Arg	Gly	Ala	Ile	Ala	Phe	Ala	Leu	Ala	Ile	Arg	Asn	Thr
	130					135					140				
Glu	Ser	Gln	Pro	Lys	Gln	Met	Met	Phe	Thr	Thr	Thr	Leu	Leu	Leu	Val
145					150					155					160
Phe	Phe	Thr	Val	Trp	Val	Phe	Gly	Gly	Gly	Thr	Thr	Pro	Met	Leu	Thr
				165					170					175	
Trp	Leu	Gln	Ile	Arg	Val	Gly	Val	Asp	Leu	Asp	Glu	Asn	Leu	Lys	Glu
			180					185					190		
Asp	Pro	Ser	Ser	Gln	His	Gln	Glu	Ala	Asn	Asn	Leu	Asp	Lys	Asn	Met
		195					200					205			
Thr	Lys	Ala	Glu	Ser	Ala	Arg	Leu	Phe	Arg	Met	Trp	Tyr	Ser	Phe	Asp
	210					215					220				
His	Lys	Tyr	Leu	Lys	Pro	Ile	Leu	Thr	His	Ser	Gly	Pro	Pro	Leu	Thr
225					230					235					240
Thr	Thr	Leu	Pro	Glu	Trp	Cys	Gly	Pro	Ile	Ser	Arg	Leu	Leu	Thr	Ser
				245					250					255	
Pro	Gln	Ala	Tyr	Gly	Glu	Gln	Leu	Lys	Glu	Asp	Asp	Val	Glu	Cys	Ile
			260					265					270		
Val	Asn	Gln	Asp	Glu	Leu	Ala	Ile	Asn	Tyr	Gln	Glu	Gln	Ala	Ser	Ser
		275					280					285			
Pro	Cys	Ser	Pro	Pro	Ala	Arg	Leu	Gly	Leu	Asp	Gln	Lys	Ala	Ser	Pro
	290					295					300				
Gln	Thr	Pro	Gly	Lys	Glu	Asn	Ile	Tyr	Glu	Gly	Asp	Leu	Gly	Leu	Gly
305					310					315					320
Gly	Tyr	Glu	Leu	Lys	Leu	Glu	Gln	Thr	Leu	Gly	Gln	Ser	Gln	Leu	Asn
				325					330					335	

&lt;210&gt; 380

&lt;211&gt; 72

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (19)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (23)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (25)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (27)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (32)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (33)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (35)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (40)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (42)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (47)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (50)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (51)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (55)  
<223> Xaa equals any of the naturally occurring L-amino acids

216

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (68)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 380

Met	Gln	Trp	Leu	Xaa	Ile	Thr	Pro	Arg	Leu	Phe	Tyr	Phe	Pro	Leu	Leu
1				5					10					15	

Leu	Leu	Xaa	Leu	Gly	Ser	Xaa	Lys	Xaa	Leu	Xaa	Ile	Ser	Ile	Leu	Xaa
			20					25					30		

Xaa	Gly	Xaa	Val	Leu	Leu	His	Xaa	Ser	Xaa	Arg	Met	His	Gly	Xaa	Asn
		35					40					45			

Met	Xaa	Xaa	Gln	Ser	Leu	Xaa	Phe	Lys	Val	Lys	Leu	Ser	Ser	Pro	Leu
	50					55					60				

Pro	Ser	Gln	Xaa	Leu	Gly	Leu	Arg
65					70		

&lt;210&gt; 381

&lt;211&gt; 75

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 381

Met	Gly	Ala	Ser	Leu	Cys	Leu	Thr	Gln	Leu	Leu	Leu	Leu	Gly	Lys
1				5					10				15	

Gly	Gly	Leu	Gly	Gln	Ala	Ser	Ile	Pro	Leu	Val	Lys	Thr	Pro	Ala	Gly
			20					25					30		

His	Gln	Ala	Phe	Trp	Thr	Arg	Thr	His	Thr	His	Thr	His	Thr	His	Thr
		35					40					45			

His	Lys	Thr	Ser	Gln	Gln	Ala	Ser	Cys	Ser	Asp	Leu	Ser	Ser	Arg	Val
	50					55					60				

Thr	Ser	Ala	Ala	Pro	Pro	Ser	His	Pro	Phe	Leu
65					70					75

&lt;210&gt; 382

&lt;211&gt; 81

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (77)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 382

Met	Cys	Val	His	Thr	Cys	Val	Cys	Met	Cys	Val	His	Thr	Cys	Val	Cys
1				5					10					15	

Val	His	Ala	Cys	Val	Trp	Ala	His	Val	Cys	Met	Cys	Val	Cys	Glu	Cys
			20					25					30		

Val	Cys	Trp	Gly	Gly	Gly	Met	Ala	Leu	Gly	Lys	Val	Cys	Pro	Gly	Trp
			35				40						45		



217

[illegible]

```

<210> 383
<211> 117
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (116)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 383
Met His Pro Pro Pro Gly Val Trp Leu Leu His Leu His Thr Pro Leu
  1          5          10          15
Arg Gly Phe Cys Leu Pro Leu Pro Leu Arg Ser Gln Glu Ala Val Pro
      20          25          30
Gly Arg Gly Arg Arg His Leu Ser Pro Gln Leu Leu Thr Pro His Pro
      35          40          45
Leu Thr Ser Ser Pro Phe Val Lys Tyr Thr Gln Asp Glu Thr Cys Thr
      50          55          60
Gln Trp Leu Thr Ala Ala Arg Phe Val Thr Ala Arg Gly Gly Glu His
      65          70          75          80
Arg Thr Pro Ser Glu Gly Glu Gly Ile Ser Thr Ala Pro Pro Pro Cys
      85          90          95
Trp Asn Glu Thr Gln Pro Gln Gly Gly Ala Thr Ser Asp Pro Gly His
      100          105          110
Ser Ala Asp Xaa Pro
      115

```

<210> 384  
<211> 167  
<212> PRT  
<213> Homo sapiens

<400> 384  
Pro Gly Pro Gly Ser Cys Leu Leu His Leu Ser Ser Gln Asn Leu Trp  
1 5 10 15  
Gln Pro Glu Phe Phe Asn Ser Leu Ser Leu Ser Leu His Gln Leu His  
20 25 30  
Ser Arg Ile Asn Arg Lys Val Ala Ala Arg Pro Ala Gly Pro Leu Val  
35 40 45  
Ser Leu Pro Leu His Leu Gly Val Ser Gln Pro Leu Pro Gly Ser Pro  
50 55 60

218

Gln Glu Ala Met Ala Pro Leu Ala Phe Val Cys Leu Ser Gly Gly Ala  
 65 70 75 80  
 Asp Ser Arg Gly Thr Cys Pro Ser Ala Ala Glu Trp Pro Pro Cys Pro  
 85 90 95  
 Ala Lys Pro Asp Val His Ser Pro Gly Ala Pro Pro Pro Pro Leu Ser  
 100 105 110  
 Cys Pro Gly Pro Trp Gly Thr Asn Ser Pro Ile Ser Thr Arg Ala Leu  
 115 120 125  
 Ala His His His Gly Thr Leu Pro Pro Arg Pro Ser Pro Pro Leu Leu  
 130 135 140  
 Cys Pro Ser Trp Pro His Leu Ala Ser Pro Gly Gly Glu Leu Ser Pro  
 145 150 155 160  
 Ala Val Pro Thr Leu Pro Pro  
 165

&lt;210&gt; 385

&lt;211&gt; 277

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 385

Arg Arg Val Val Ile Asp Pro Gln Glu Lys Pro Ser Glu Glu Pro Leu  
 1 5 10 15  
 Gly Asp Arg Arg Thr Val Ile Asp Lys Cys Ser Pro Pro Leu Glu Phe  
 20 25 30  
 Leu Asp Asp Ser Asp Ser His Leu Glu Ile Gln Lys His Lys Asp Arg  
 35 40 45  
 Glu Val Val Met Glu His Pro Ser Ser Gly Ser Asp Trp Ser Asp Val  
 50 55 60  
 Glu Glu Ile Ser Thr Val Arg Phe Ser Gln Glu Glu Pro Val Ser Leu  
 65 70 75 80  
 Lys Pro Ser Ala Val Pro Glu Pro Ser Ser Phe Thr Thr Asp Tyr Val  
 85 90 95  
 Met Tyr Pro Pro His Leu Tyr Ser Ser Pro Trp Cys Asp Tyr Ala Ser  
 100 105 110  
 Tyr Trp Thr Ser Ser Pro Lys Pro Ser Ser Tyr Pro Ser Thr Gly Ser  
 115 120 125  
 Ser Ser Asn Asp Ala Ala Gln Val Gly Lys Ser Ser Arg Ser Arg Met  
 130 135 140  
 Ser Asp Tyr Ser Pro Asn Ser Thr Gly Ser Val Gln Asn Thr Ser Arg  
 145 150 155 160  
 Asp Met Glu Ala Ser Glu Glu Gly Trp Ser Gln Asn Ser Arg Ser Phe  
 165 170 175  
 Arg Phe Ser Arg Ser Ser Glu Glu Arg Glu Val Lys Glu Lys Arg Thr  
 180 185 190  
 Phe Gln Glu Glu Met Pro Pro Arg Pro Cys Gly Gly His Ala Ser Ser

219

195					200					205					
Ser	Leu	Pro	Lys	Ser	His	Leu	Glu	Pro	Ser	Leu	Glu	Glu	Gly	Phe	Ile
210						215					220				
Asp	Thr	His	Cys	His	Leu	Asp	Met	Leu	Tyr	Ser	Lys	Leu	Ser	Phe	Gln
225					230					235					240
Gly	Thr	Phe	Thr	Lys	Phe	Arg	Lys	Ile	Tyr	Ser	Ser	Ser	Phe	Pro	Lys
				245					250					255	
Glu	Phe	Gln	Gly	Cys	Ile	Ser	Asp	Phe	Cys	Val	Arg	Gly	Gly	Lys	Ala
			260					265					270		
Glu	Met	Thr	Trp	Lys											
				275											

&lt;210&gt; 386

&lt;211&gt; 172

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (153)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 386

Trp	Phe	Ala	Ala	Leu	Val	Lys	Cys	Leu	Pro	Val	Leu	Cys	Leu	Ala	Gly
1				5					10					15	

Phe	Leu	Trp	Val	Met	Ser	Pro	Ser	Gly	Gly	Tyr	Thr	Gln	Leu	Leu	Gln
			20					25					30		

Gly	Ala	Leu	Val	Cys	Ser	Ala	Val	Gly	Asp	Ala	Cys	Leu	Ile	Trp	Pro
		35					40					45			

Ala	Ala	Phe	Val	Pro	Gly	Met	Ala	Ala	Phe	Ala	Thr	Ala	His	Leu	Leu
	50					55					60				

Tyr	Val	Trp	Ala	Phe	Gly	Phe	Ser	Pro	Leu	Gln	Pro	Gly	Leu	Leu	Leu
65					70					75					80

Leu	Ile	Ile	Leu	Ala	Pro	Gly	Pro	Tyr	Leu	Ser	Leu	Val	Leu	Gln	His
				85					90					95	

Leu	Glu	Pro	Asp	Met	Val	Leu	Pro	Val	Ala	Ala	Tyr	Gly	Leu	Ile	Leu
			100					105					110		

Met	Ala	Met	Leu	Trp	Arg	Gly	Leu	Ala	Gln	Gly	Gly	Ser	Ala	Gly	Trp
		115					120					125			

Gly	Ala	Leu	Leu	Phe	Thr	Leu	Ser	Asp	Gly	Val	Leu	Ala	Trp	Asp	Thr
	130					135					140				

Phe	Ala	Gln	Pro	Leu	Pro	His	Ala	Xaa	Leu	Val	Ile	Met	Thr	Thr	Tyr
145					150					155					160

Tyr	Ala	Ala	Gln	Leu	Leu	Ile	Thr	Leu	Ser	Ala	Leu
				165					170		

&lt;210&gt; 387

&lt;211&gt; 156

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

220

&lt;400&gt; 387

Arg Pro Gly Ala Asp Cys Glu Val Cys Lys Glu Phe Leu Asn Arg Phe  
 1 5 10 15  
 Tyr Lys Ser Leu Ile Asp Arg Gly Val Asn Phe Ser Leu Asp Thr Ile  
 20 25 30  
 Glu Lys Glu Leu Ile Ser Phe Cys Leu Asp Thr Lys Gly Lys Glu Asn  
 35 40 45  
 Arg Leu Cys Tyr Tyr Leu Gly Ala Thr Lys Asp Ala Ala Thr Lys Ile  
 50 55 60  
 Leu Ser Glu Val Thr Arg Pro Met Ser Val His Met Pro Ala Met Lys  
 65 70 75 80  
 Ile Cys Glu Lys Leu Lys Lys Leu Asp Ser Gln Ile Cys Glu Leu Lys  
 85 90 95  
 Tyr Glu Lys Thr Leu Asp Leu Ala Ser Val Asp Leu Arg Lys Met Arg  
 100 105 110  
 Val Ala Glu Leu Lys Gln Ile Leu His Ser Trp Gly Glu Glu Cys Arg  
 115 120 125  
 Ala Cys Ala Glu Lys Thr Asp Tyr Val Asn Leu Ile Gln Glu Leu Ala  
 130 135 140  
 Pro Lys Tyr Ala Ala Thr His Pro Lys Thr Glu Leu  
 145 150 155

&lt;210&gt; 388

&lt;211&gt; 268

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

Phe Phe Ser Val Tyr Ala Gln Leu Trp Leu Val Leu Leu Tyr Gly His  
 1 5 10 15  
 Lys Arg Leu Ser Tyr Gln Thr Val Phe Leu Ala Leu Cys Leu Leu Trp  
 20 25 30  
 Ala Ala Leu Arg Thr Thr Leu Phe Ser Phe Tyr Phe Arg Asp Thr Pro  
 35 40 45  
 Arg Ala Asn Arg Leu Gly Pro Leu Pro Phe Trp Leu Leu Tyr Cys Cys  
 50 55 60  
 Pro Val Cys Leu Gln Phe Phe Thr Leu Thr Leu Met Asn Leu Tyr Phe  
 65 70 75 80  
 Ala Gln Val Val Phe Lys Ala Lys Val Lys Arg Arg Pro Glu Met Ser  
 85 90 95  
 Arg Gly Leu Leu Ala Val Arg Gly Ala Phe Val Gly Ala Ser Leu Leu  
 100 105 110  
 Phe Leu Leu Val Asn Val Leu Cys Ala Val Leu Ser His Arg Arg Arg  
 115 120 125  
 Ala Gln Pro Trp Ala Leu Leu Leu Val Arg Val Leu Val Ser Asp Ser  
 130 135 140  
 Leu Phe Val Ile Cys Ala Leu Ser Leu Ala Ala Cys Leu Cys Leu Val  
 145 150 155 160

Ala	Arg	Arg	Ala	Pro 165	Ser	Thr	Ser	Ile	Tyr 170	Leu	Glu	Ala	Lys	Gly 175	Thr
Ser	Val	Cys	Gln 180	Ala	Ala	Ala	Met	Gly 185	Gly	Ala	Met	Val	Leu 190	Leu	Tyr
Ala	Ser	Arg 195	Ala	Cys	Tyr	Asn	Leu 200	Thr	Ala	Leu	Ala	Leu 205	Ala	Pro	Gln
Ser	Arg 210	Leu	Asp	Thr	Phe	Asp 215	Tyr	Asp	Trp	Tyr	Asn 220	Val	Ser	Asp	Gln
Ala 225	Asp	Leu	Val	Asn	Asp 230	Leu	Gly	Asn	Lys	Gly 235	Tyr	Leu	Val	Phe	Gly 240
Leu	Ile	Leu	Phe	Val 245	Trp	Glu	Leu	Leu	Pro 250	Thr	Thr	Leu	Leu	Val 255	Gly
Phe	Phe	Arg	Val 260	His	Arg	Pro	Pro	Gln 265	Asp	Leu	Ser				

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<210> 389
<211> 222
<212> PRT
<213> Homo sapiens
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<400>	389															
Ser 1	Glu	Lys	Arg	Tyr 5	Pro	Gln	Pro	Arg	Gly 10	Gln	Lys	Lys	Lys	Lys	Val 15	
Val	Lys	Tyr	Gly 20	Met	Gly	Gly	Met	Ile 25	Ile	Val	Leu	Leu	Ile 30	Cys	Ile	
Val	Trp	Phe 35	Pro	Leu	Leu	Phe	Met 40	Ser	Leu	Ile	Lys	Ser 45	Val	Ala	Gly	
Val	Ile 50	Asn	Gln	Pro	Leu	Asp 55	Val	Ser	Val	Thr	Ile 60	Thr	Leu	Gly	Gly	
Tyr 65	Gln	Pro	Ile	Phe	Thr 70	Met	Ser	Ala	Gln	Gln 75	Ser	Gln	Leu	Lys	Ile 80	
Met	Asp	Gln	Gln	Ser 85	Phe	Asn	Lys	Phe	Ile 90	Gln	Ala	Phe	Ser	Arg 95	Asp	
Thr	Gly	Ala	Met 100	Gln	Phe	Leu	Glu	Asn 105	Tyr	Glu	Lys	Glu	Asp 110	Ile	Thr	
Val	Ala	Glu 115	Leu	Glu	Gly	Asn	Ser 120	Asn	Ser	Leu	Trp	Thr 125	Ile	Ser	Pro	
Pro	Ser 130	Lys	Gln	Lys	Met	Ile 135	His	Glu	Leu	Leu	Asp 140	Pro	Asn	Ser	Ser	
Phe 145	Ser	Val	Val	Phe	Ser 150	Trp	Ser	Ile	Gln	Arg 155	Asn	Leu	Ser	Leu	Gly 160	
Ala	Lys	Ser	Glu	Ile 165	Ala	Thr	Asp	Lys	Leu 170	Ser	Phe	Pro	Leu	Lys 175	Asn	
Ile	Thr	Arg	Lys 180	Asn	Ile	Ala	Lys	Met 185	Ile	Ala	Gly	Asn	Ser 190	Thr	Glu	
Ser	Ser	Lys 195	Thr	Pro	Val	Thr	Ile 200	Glu	Lys	Ile	Tyr	Pro 205	Tyr	Tyr	Val	

222

Lys Ala Pro Ser Asp Ser Asn Ser Lys Pro Ile Lys Gln Leu  
 210 215 220  
 <210> 390  
 <211> 267  
 <212> PRT  
 <213> Homo sapiens  
 <400> 390  
 Thr Asp Gly Glu Ser Arg Phe Tyr Ser Leu Gly His Leu Ser Ile Gln  
 1 5 10 15  
 Arg Ala Ala Leu Val Val Leu Glu Asn Tyr Tyr Lys Asp Phe Thr Ile  
 20 25 30  
 Tyr Asn Pro Asn Leu Leu Thr Ala Ser Lys Phe Arg Ala Ala Lys His  
 35 40 45  
 Met Ala Gly Leu Lys Val Tyr Asn Val Asp Gly Pro Ser Asn Asn Ala  
 50 55 60  
 Thr Gly Gln Ser Arg Ala Met Ile Ala Ala Ala Arg Arg Arg Asp  
 65 70 75 80  
 Ser Ser His Asn Glu Leu Tyr Tyr Glu Glu Ala Glu His Glu Arg Arg  
 85 90 95  
 Val Lys Lys Arg Lys Ala Arg Leu Val Val Ala Val Glu Glu Ala Phe  
 100 105 110  
 Ile His Ile Gln Arg Leu Gln Ala Glu Glu Gln Gln Lys Ala Pro Gly  
 115 120 125  
 Glu Val Met Asp Pro Arg Glu Ala Ala Gln Ala Ile Phe Pro Ser Met  
 130 135 140  
 Ala Arg Ala Leu Gln Lys Tyr Leu Arg Ile Thr Arg Gln Gln Asn Tyr  
 145 150 155 160  
 His Ser Met Glu Ser Ile Leu Gln His Leu Ala Phe Cys Ile Thr Asn  
 165 170 175  
 Gly Met Thr Pro Lys Ala Phe Leu Glu Arg Tyr Leu Ser Ala Gly Pro  
 180 185 190  
 Thr Leu Gln Tyr Asp Lys Asp Arg Trp Leu Ser Thr Gln Trp Arg Leu  
 195 200 205  
 Val Ser Asp Glu Ala Leu Thr Asn Gly Leu Arg Asp Gly Ile Val Phe  
 210 215 220  
 Val Leu Lys Cys Leu Asp Phe Ser Leu Val Val Asn Val Lys Lys Ile  
 225 230 235 240  
 Pro Phe Ile Ile Leu Ser Glu Glu Phe Ile Asp Pro Lys Ser His Lys  
 245 250 255  
 Phe Val Leu Arg Leu Gln Ser Glu Thr Ser Val  
 260 265

<210> 391  
 <211> 97  
 <212> PRT  
 <213> Homo sapiens

223

&lt;400&gt; 391

Gln Ser Cys Tyr Val Ala Gln Ala Gly Val Gln Trp His Asn His Ser  
 1 5 10 15  
 Ser Leu Gln Pro Leu Ser Pro Gly Phe Lys Arg Phe Phe Cys Leu Asn  
 20 25 30  
 Leu Pro Ser Ser Trp Asp Tyr Arg His Met Ala Thr Cys Pro Trp Leu  
 35 40 45  
 Ile Phe Val Phe Leu Val Glu Met Glu Phe Arg His Val Gly Gln Ala  
 50 55 60  
 Gly Leu Gly Leu Leu Thr Ser Ser Asp Leu Pro Ala Leu Ala Phe Gln  
 65 70 75 80  
 Ser Ala Gly Ile Thr Gly Leu Ser His His Ala Trp Pro Gly Arg Phe  
 85 90 95

Leu

&lt;210&gt; 392

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (28)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (43)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 392

Phe Phe Val Phe Leu Val Glu Met Gly Phe Arg His Val Gly Gln Xaa  
 1 5 10 15

Gly Leu Glu Leu Leu Thr Ser Gly Tyr Pro Ser Xaa Leu Thr Ser Gln  
 20 25 30

Ser Ala Gly Ile Thr Gly Met Ser His His Xaa Arg  
 35 40

&lt;210&gt; 393

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 393

Gln Gly Ser Cys Leu Ser Leu Pro Ser Ser Trp Gly Tyr Arg Cys Pro  
 1 5 10 15

Pro Pro His Pro Gly Asn Phe Leu Tyr  
 20 25

&lt;210&gt; 394

&lt;211&gt; 25

224

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 394

Met	Phe	Phe	Cys	Phe	Xaa	Arg	Trp	Glu	Pro	Cys	Ser	Val	Thr	Gln	Ala
1				5					10					15	

Gly	Val	Gln	Trp	Cys	Asp	Leu	Ser	Ser
		20						25

&lt;210&gt; 395

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 395

Pro	Ala	Ser	Ala	Ser	Arg	Val	Ala	Gly	Val	Thr	Gly	Ala	Pro	His	His
1				5					10					15	

Thr Gln

&lt;210&gt; 396

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 396

Leu	Xaa	Lys	Cys	Trp	Asp	Tyr	Arg	Tyr	Glu	Pro	Pro	Arg	Pro	Ala
1				5					10					15

&lt;210&gt; 397

&lt;211&gt; 157

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (141)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 397

Val	Asn	Pro	Glu	Val	Trp	Met	Asn	Thr	Ser	Glu	Ile	Ile	Ile	Tyr	Asn
1				5					10					15	

Gly	Tyr	Pro	Ser	Glu	Glu	Tyr	Glu	Val	Thr	Thr	Glu	Asp	Gly	Tyr	Ile
			20					25					30		

Leu	Leu	Val	Asn	Arg	Ile	Pro	Tyr	Gly	Arg	Thr	His	Ala	Arg	Ser	Thr
		35					40					45			

Gly	Pro	Arg	Pro	Val	Val	Tyr	Met	Gln	His	Ala	Leu	Phe	Ala	Asp	Asn
	50					55					60				

Ala	Tyr	Trp	Leu	Glu	Asn	Tyr	Ala	Asn	Gly	Ser	Leu	Gly	Phe	Leu	Leu
65					70					75					80



225

Ala Asp Ala Gly Tyr Asp Val Trp Met Gly Asn Ser Arg Gly Asn Thr  
85 90 95

Trp Ser Arg Arg His Lys Thr Leu Ser Glu Thr Asp Glu Lys Phe Trp  
100 105 110

Ala Phe Ser Phe Asp Glu Met Ala Lys Tyr Asp Leu Pro Gly Val Ile  
115 120 125

Asp Phe Ile Val Asn Lys Thr Gly Gln Glu Lys Leu Xaa Phe Ile Gly  
130 135 140

His Ser Leu Gly Thr Thr Ile Gly Phe Val Ala Phe Ser  
145 150 155

<210> 398

<211> 16

<212> PRT

<213> Homo sapiens

<400> 398

Met Pro Glu Leu Ala Gln Arg Ile Lys Met Asn Phe Ala Leu Gly Pro  
1 5 10 15

<210> 399

<211> 75

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (55)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 399

Phe Phe Leu Arg Gln Cys Leu Ile Leu Leu Pro Arg Leu Glu Cys Ser  
1 5 10 15

Gly Met Ser Ile Thr His Cys Ser Leu Asp Leu Leu Gly Ser Ser Asn  
20 25 30

Pro Pro Thr Ser Val Ser His Val Val Trp Thr Thr Gly Thr His His  
35 40 45

Arg Asp Trp Leu Ile Phe Xaa Phe Phe Val Glu Met Glu Ser His Phe  
50 55 60

Phe Ala Gln Ala Gly Trp Ser Xaa Leu Asn Ser  
65 70 75

<210> 400

<211> 28

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

226

&lt;222&gt; (6)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 400

Ile	Lys	Phe	Leu	Gly	Xaa	Ser	Asp	Pro	Pro	Ile	Leu	Cys	Ser	Gln	Ser
1				5					10					15	

Ala	Gly	Ile	Thr	Gly	Met	Ser	His	Cys	Ala	His	Pro
			20					25			

&lt;210&gt; 401

&lt;211&gt; 237

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (226)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 401

Lys	Ser	Ser	Asp	Gly	Pro	Gly	Ala	Ala	Gln	Glu	Pro	Thr	Trp	Leu	Thr
1				5					10					15	

Asp	Val	Pro	Ala	Ala	Met	Glu	Phe	Ile	Ala	Ala	Thr	Glu	Val	Ala	Val
			20					25					30		

Ile	Gly	Phe	Phe	Gln	Asp	Leu	Glu	Ile	Pro	Ala	Val	Pro	Ile	Leu	His
		35					40					45			

Ser	Met	Val	Gln	Lys	Phe	Pro	Gly	Val	Ser	Phe	Gly	Ile	Ser	Thr	Asp
	50					55					60				

Ser	Glu	Val	Leu	Thr	His	Tyr	Asn	Ile	Thr	Gly	Asn	Thr	Ile	Cys	Leu
65					70					75					80

Phe	Arg	Leu	Val	Asp	Asn	Glu	Gln	Leu	Asn	Leu	Glu	Asp	Glu	Asp	Ile
				85					90					95	

Glu	Ser	Ile	Asp	Ala	Thr	Lys	Leu	Ser	Arg	Phe	Ile	Glu	Ile	Asn	Ser
			100					105					110		

Leu	His	Met	Val	Thr	Glu	Tyr	Asn	Pro	Val	Ala	Ser	Pro	Glu	Tyr	Glu
		115					120					125			

Glu	Asn	Met	His	Arg	Tyr	Gln	Lys	Ala	Ala	Lys	Leu	Phe	Gln	Gly	Lys
	130					135					140				

Ile	Leu	Phe	Ile	Leu	Val	Asp	Ser	Gly	Met	Lys	Glu	Asn	Gly	Lys	Val
145					150					155					160

Ile	Ser	Phe	Phe	Lys	Leu	Lys	Glu	Ser	Gln	Leu	Pro	Ala	Leu	Ala	Ile
				165					170					175	

Tyr	Gln	Thr	Leu	Asp	Asp	Glu	Trp	Asp	Thr	Leu	Pro	Thr	Ala	Glu	Val
			180					185					190		

Ser	Val	Glu	His	Val	Gln	Asn	Phe	Cys	Asp	Gly	Phe	Leu	Ser	Gly	Lys
		195					200					205			

Leu	Leu	Lys	Glu	Asn	Arg	Glu	Ser	Glu	Gly	Lys	Thr	Pro	Lys	Val	Glu
	210					215					220				

Leu	Xaa	Leu	Leu	Leu	Gly	Thr	Thr	Tyr	Gly	Gln	Val	Ser
225					230					235		

227

<210> 402  
 <211> 209  
 <212> PRT  
 <213> Homo sapiens

<400> 402  
 Asp Gly Ala Asp Val Asn Tyr Gln Ser Lys Glu Gly Lys Ser Pro Leu  
     1                    5                    10                    15  
 His Met Ala Ala Ile His Gly Arg Phe Thr Arg Ser Gln Ile Leu Ile  
                     20                    25                    30  
 Gln Asn Gly Ser Glu Ile Asp Cys Ala Asp Lys Phe Gly Asn Thr Pro  
                     35                    40                    45  
 Leu His Val Ala Ala Arg Tyr Gly His Glu Leu Leu Ile Ser Thr Leu  
       50                    55                    60  
 Met Thr Asn Gly Ala Asp Thr Ala Arg Arg Gly Ile His Asp Met Phe  
     65                    70                    75                    80  
 Pro Leu His Leu Ala Val Leu Phe Gly Phe Ser Asp Cys Cys Arg Lys  
                     85                    90                    95  
 Leu Leu Ser Ser Gly Gln Leu Tyr Ser Ile Val Ser Ser Leu Ser Asn  
                     100                    105                    110  
 Glu His Val Leu Ser Ala Gly Phe Asp Ile Asn Thr Pro Asp Asn Leu  
       115                    120                    125  
 Gly Arg Thr Cys Leu His Ala Ala Ala Ser Gly Gly Asn Val Glu Cys  
     130                    135                    140  
 Leu Asn Leu Leu Leu Ser Ser Gly Ala Asp Leu Arg Arg Arg Asp Lys  
   145                    150                    155                    160  
 Phe Gly Arg Thr Pro Leu His Tyr Ala Ala Ala Asn Gly Ser Tyr Gln  
                     165                    170                    175  
 Cys Ala Val Thr Leu Val Thr Ala Gly Ala Gly Val Asn Glu Ala Asp  
                     180                    185                    190  
 Cys Lys Gly Cys Ser Pro Leu His Tyr Ala Ala Ala Ser Asp Thr Tyr  
     195                    200                    205

Arg

<210> 403  
 <211> 192  
 <212> PRT  
 <213> Homo sapiens

<400> 403  
 Lys Ser Pro Leu His Met Ala Ala Ile His Gly Arg Phe Thr Arg Ser  
     1                    5                    10                    15  
 Gln Ile Leu Ile Gln Asn Gly Ser Glu Ile Asp Cys Ala Asp Lys Phe  
                     20                    25                    30  
 Gly Asn Thr Pro Leu His Val Ala Ala Arg Tyr Gly His Glu Leu Leu  
     35                    40                    45  
 Ile Ser Thr Leu Met Thr Asn Gly Ala Asp Thr Ala Arg Arg Gly Ile  
     50                    55                    60

228

His Asp Met Phe Pro Leu His Leu Ala Val Leu Phe Gly Phe Ser Asp  
 65 70 75 80  
 Cys Cys Arg Lys Leu Leu Ser Ser Gly Gln Leu Tyr Ser Ile Val Ser  
 85 90 95  
 Ser Leu Ser Asn Glu His Val Leu Ser Ala Gly Phe Asp Ile Asn Thr  
 100 105 110  
 Pro Asp Asn Leu Gly Arg Thr Cys Leu His Ala Ala Ala Ser Gly Gly  
 115 120 125  
 Asn Val Glu Cys Leu Asn Leu Leu Leu Ser Ser Gly Ala Asp Leu Arg  
 130 135 140  
 Arg Arg Asp Lys Phe Gly Arg Thr Pro Leu His Tyr Ala Ala Ala Asn  
 145 150 155 160  
 Gly Ser Tyr Gln Cys Ala Val Thr Leu Val Thr Ala Gly Ala Gly Val  
 165 170 175  
 Asn Glu Ala Asp Cys Lys Gly Cys Ser Pro Leu His Tyr Ala Ala Ala  
 180 185 190

&lt;210&gt; 404

&lt;211&gt; 270

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (252)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 404

Met Gly Pro Pro Pro Gly Ala Gly Val Ser Cys Arg Gly Gly Cys Gly  
 1 5 10 15  
 Phe Ser Arg Leu Leu Ala Trp Cys Phe Leu Leu Ala Leu Ser Pro Gln  
 20 25 30  
 Ala Pro Gly Ser Arg Gly Ala Glu Ala Val Trp Thr Ala Tyr Leu Asn  
 35 40 45  
 Val Ser Trp Arg Val Pro His Thr Gly Val Asn Arg Thr Val Trp Glu  
 50 55 60  
 Leu Ser Glu Glu Gly Val Tyr Gly Gln Asp Ser Pro Leu Glu Pro Val  
 65 70 75 80  
 Ala Gly Val Leu Val Pro Pro Asp Gly Pro Gly Ala Leu Asn Ala Cys  
 85 90 95  
 Asn Pro His Thr Asn Phe Thr Val Pro Thr Val Trp Gly Ser Thr Val  
 100 105 110  
 Gln Val Ser Trp Leu Ala Leu Ile Gln Arg Gly Gly Gly Cys Thr Phe  
 115 120 125  
 Ala Asp Lys Ile His Leu Ala Tyr Glu Arg Gly Ala Ser Gly Ala Val  
 130 135 140  
 Ile Phe Asn Phe Pro Gly Thr Arg Asn Glu Val Ile Pro Met Ser His

229

145		150		155		160
Pro Gly Ala Val	Asp 165	Ile Val Ala Ile	Met 170	Ile Gly Asn Leu	Lys 175	Gly
Thr Lys Ile	Leu 180	Gln Ser Ile Gln	Arg 185	Gly Ile Gln Val	Thr 190	Met Val
Ile Glu Val	Gly 195	Lys Lys His	Gly 200	Pro Trp Val Asn	His 205	Tyr Ser Ile
Phe Phe Arg Phe	Cys 210	Val Leu Phe	Tyr 215	Tyr Tyr Gly	Gly 220	Asn Cys Gly
Leu Phe Tyr Leu	Leu 225	Phe Cys Ser Lys	Ala 230	Thr Glu Cys Lys	Ser 235	Ser Ser
Lys Gln Glu Ala	Glu 245	Ala Ile Lys	Gly 250	Arg Cys Xaa Lys	Ser 255	Tyr Trp
Lys Ala Ser Thr	Thr 260	His Thr Glu	Thr 265	Arg Arg Gln Gly	Asn 270	

&lt;210&gt; 405

&lt;211&gt; 63

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (43)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 405

Phe Phe Tyr Phe	Tyr 5	Phe Leu Arg Trp	Ser 10	Leu Gly Leu Leu	Pro 15	Arg
-----------------	----------	-----------------	-----------	-----------------	-----------	-----

Leu Glu Cys Ser	Gly 20	Thr Ile Ser Ala	His 25	Cys Lys Leu Arg	Leu 30	Pro
-----------------	-----------	-----------------	-----------	-----------------	-----------	-----

Asp Thr Asn Asn	Ser 35	Pro Ala Ser Ala	Ser 40	Xaa Val Ala Gly	Ile 45	Thr
-----------------	-----------	-----------------	-----------	-----------------	-----------	-----

Gly Ala Cys His	His 50	Ala Trp Leu	Ile 55	Phe Leu Phe	Leu 60	Val Asp
-----------------	-----------	-------------	-----------	-------------	-----------	---------

&lt;210&gt; 406

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 406

Lys Gly Cys Leu	Pro 5	Phe Ser Ser Ser	Ser 10	Ser Trp Pro Gly	Val 15	Pro
-----------------	----------	-----------------	-----------	-----------------	-----------	-----

Thr Leu Ala Ser	Leu 20	Phe Gly Arg Leu	Trp 25	Phe
-----------------	-----------	-----------------	-----------	-----

&lt;210&gt; 407

&lt;211&gt; 92

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 407

Ile Ser Asp Leu	Val 5	Gly Arg Val Val	Ser 10	Gly Trp Leu Gly	Asp 15	Ala
-----------------	----------	-----------------	-----------	-----------------	-----------	-----

230

Val Pro Gly Pro Val Thr Arg Leu Leu Met Leu Trp Thr Thr Leu Thr  
                   20                  25                  30  
 Gly Val Ser Leu Ala Leu Phe Pro Val Ala Gln Ala Pro Thr Ala Leu  
                   35                  40                  45  
 Val Ala Leu Ala Val Ala Tyr Gly Phe Thr Ser Gly Ala Leu Ala Pro  
                   50                  55                  60  
 Leu Ala Phe Ser Val Leu Pro Glu Leu Ile Gly Thr Arg Arg Ile Tyr  
                   65                  70                  75                  80  
 Cys Gly Leu Gly Leu Leu Gln Met Ile Glu Ser Ile  
                   85                  90

&lt;210&gt; 408

&lt;211&gt; 221

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (176)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 408

Arg Phe Glu Phe Cys Glu Pro Ala Phe Val Val Gly Asn Cys Leu Gln  
   1                  5                  10                  15  
 Ile Ala Ser Asp Ser His Gln Tyr Asp Arg Ile Tyr Cys Gly Ala Gly  
                   20                  25                  30  
 Val Gln Lys Asp His Glu Asn Tyr Met Lys Ile Leu Leu Lys Val Gly  
                   35                  40                  45  
 Gly Ile Leu Val Met Pro Ile Glu Asp Gln Leu Thr Gln Ile Met Arg  
                   50                  55                  60  
 Thr Gly Gln Asn Thr Trp Glu Ser Lys Asn Ile Leu Ala Val Ser Phe  
                   65                  70                  75                  80  
 Ala Pro Leu Val Gln Pro Ser Lys Asn Asp Asn Gly Lys Pro Asp Ser  
                   85                  90                  95  
 Val Gly Leu Pro Pro Cys Ala Val Arg Asn Leu Gln Asp Leu Ala Arg  
                   100                  105                  110  
 Ile Tyr Ile Arg Arg Thr Leu Arg Asn Phe Ile Asn Asp Glu Met Gln  
                   115                  120                  125  
 Ala Lys Gly Ile Pro Gln Arg Ala Pro Pro Lys Arg Lys Arg Lys Arg  
                   130                  135                  140  
 Val Lys Gln Arg Ile Asn Thr Tyr Val Phe Val Gly Asn Gln Leu Ile  
                   145                  150                  155                  160  
 Pro Gln Pro Leu Asp Ser Glu Glu Asp Glu Lys Met Glu Glu Asp Xaa  
                   165                  170                  175  
 Lys Glu Glu Glu Glu Lys Asp His Asn Glu Ala Met Lys Pro Glu Glu  
                   180                  185                  190  
 Pro Pro Gln Asn Leu Leu Arg Glu Lys Ile Met Lys Leu Pro Leu Pro  
                   195                  200                  205

231

Glu Ser Leu Lys Ala Tyr Leu Thr Tyr Phe Arg Asp Lys  
 210 215 220

<210> 409

<211> 137

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (136)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 409

Leu Phe Ser Cys His Arg Ser Glu Lys Thr Cys Arg Arg Trp Met Ala  
 1 5 10 15

Leu Asp Tyr Ala Gly Ile Ser Ile Gly Ile Leu Gly Cys Tyr Val Ser  
 20 25 30

Gly Val Phe Tyr Ala Phe Tyr Cys Asn Asn Tyr Trp Arg Gln Val Tyr  
 35 40 45

Leu Ile Thr Val Leu Ala Met Ile Leu Ala Val Phe Phe Ala Gln Ile  
 50 55 60

His Pro Asn Tyr Leu Thr Gln Gln Trp Gln Arg Leu Arg Ser Ile Ile  
 65 70 75 80

Phe Cys Ser Val Ser Gly Tyr Gly Val Ile Pro Thr Leu His Trp Val  
 85 90 95

Trp Leu Asn Gly Gly Ile Gly Ala Pro Ile Val Gln Asp Phe Ala Pro  
 100 105 110

Arg Val Ile Val Met Tyr Met Ile Ala Leu Leu Ala Phe Leu Phe Tyr  
 115 120 125

Ile Ser Lys Val Pro Glu Arg Xaa Phe  
 130 135

<210> 410

<211> 121

<212> PRT

<213> Homo sapiens

<400> 410

Glu Thr Ala Ala Glu Tyr Val Lys Ser Arg Leu Pro Glu Ala Leu Lys  
 1 5 10 15

Gln His Leu Gln Asp Tyr Glu Lys Asp Lys Glu Asn Ser Val Leu Ser  
 20 25 30

Tyr Gln Thr Ile Leu Glu Gln Gln Ile Leu Ser Ile Asp Arg Glu Met  
 35 40 45

Leu Glu Lys Leu Thr Val Ser Tyr Asp Glu Ala Gly Thr Thr Cys Leu  
 50 55 60

Ile Ala Leu Leu Ser Asp Lys Asp Leu Thr Val Ala Asn Val Gly Asp  
 65 70 75 80

Ser Arg Gly Val Leu Cys Asp Lys Asp Gly Asn Ala Ile Pro Leu Ser  
 85 90 95

His Asp His Lys Pro Tyr Gln Leu Lys Glu Arg Lys Arg Ile Lys Arg

232

100 105 110  
 Ala Gly Gly Phe Ile Ser Phe Asn Gly  
     115                      120  
 <210> 411  
 <211> 37  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (19)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <400> 411  
 Ala His Cys Ser Leu Lys Leu Pro Gly Ser Ser His Pro Leu Ala Ser  
   1                      5                      10                      15  
 Ala Ser Xaa Val Ala Gly Ile Thr Gly Val His His Cys His Thr Gln  
                     20                      25                      30  
 Leu Ile Phe Asn Phe  
                     35  
 <210> 412  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (36)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <400> 412  
 Asp Thr Glu Phe His Ser Val Thr Gln Ala Gly Val Glu Trp Cys His  
   1                      5                      10                      15  
 Leu Ser Ser Leu Gln Pro Leu Pro Pro Gly Phe Lys Gln Phe Ser Cys  
                     20                      25                      30  
 Leu Ser Leu Xaa Ser Ser Trp Asp Tyr Arg His Val Pro Pro Cys Leu  
                     35                      40                      45  
 Ala Asn Phe Cys Ile Phe  
                     50  
 <210> 413  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (32)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <400> 413  
 His Ser Val Thr Gln Ala Gly Val Glu Trp Cys His Leu Ser Ser Leu  
   1                      5                      10                      15  
 Gln Pro Leu Pro Pro Gly Phe Lys Gln Phe Ser Cys Leu Ser Leu Xaa  
                     20                      25                      30  
 Ser Ser Trp Asp Tyr Arg His Val Pro Pro Cys Leu Ala Asn Phe Cys



. 233

35                                      40                                      45  
 Ile Phe  
     50  
 <210> 414  
 <211> 94  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <400> 414  
 Ser Thr His Cys Asn Leu Arg Leu Leu Gly Ser Ser Asp Ser Pro Ala  
     1                                      5                                      10                                      15  
 Ser Ala Ser Arg Val Ala Gly Val Thr Gly Met Cys His His Ala Gln  
                                     20                                      25                                      30  
 Leu Ile Phe Val Leu Leu Val Glu Thr Gly Phe Cys His Val Gly Gln  
                                     35                                      40                                      45  
 Ala Gly Leu Glu Leu Leu Thr Ser His Asp Leu Arg Thr Xaa Ala Ser  
     50                                      55                                      60  
 Gln Ser Val Gly Ile Thr Gly Val Ser His Arg Thr Arg Pro Gly Leu  
     65                                      70                                      75                                      80  
 Pro Leu Cys Thr Tyr Phe Val Glu Ala Glu Leu Arg Pro Gly  
                                     85                                      90  
 <210> 415  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (7)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (23)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <400> 415  
 Pro Tyr Leu Pro His Phe Xaa Ile Phe Cys Arg Asp Gly Val Ser Leu  
     1                                      5                                      10                                      15  
 Cys Cys Pro Gly Trp Ser Xaa Thr Pro Glu Phe Lys Gln Ser Ser Ala  
                                     20                                      25                                      30  
 Leu Ala  
 <210> 416  
 <211> 13  
 <212> PRT  
 <213> Homo sapiens  
 <400> 416  
 Glu Cys Trp Asp Tyr Arg His Glu Pro Ser Cys Leu Ala

234

1                      5                      10  
 <210> 417  
 <211> 7  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 417  
 Leu Pro Lys Cys Trp Ser Ala  
   1                      5  
  
 <210> 418  
 <211> 317  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 418  
 Val Ala Val Leu Cys Val Cys Asp Leu Ser Pro Ala Gln Cys Asp Ile  
   1                      5                      10                      15  
  
 Asn Cys Cys Cys Asp Pro Asp Cys Ser Ser Val Asp Phe Ser Val Phe  
                     20                      25                      30  
  
 Ser Ala Cys Ser Val Pro Val Val Thr Gly Asp Ser Gln Phe Cys Ser  
                     35                      40                      45  
  
 Gln Lys Ala Val Ile Tyr Ser Leu Asn Phe Thr Ala Asn Pro Pro Gln  
   50                      55                      60  
  
 Arg Val Phe Glu Leu Val Asp Gln Ile Asn Pro Ser Ile Phe Cys Ile  
   65                      70                      75                      80  
  
 His Ile Thr Asn Tyr Lys Pro Ala Leu Ser Phe Ile Asn Pro Glu Val  
                     85                      90                      95  
  
 Pro Asp Glu Asn Asn Phe Asp Thr Leu Met Lys Thr Ser Asp Gly Phe  
                     100                      105                      110  
  
 Thr Leu Asn Ala Glu Ser Tyr Val Ser Phe Thr Thr Lys Leu Asp Ile  
   115                      120                      125  
  
 Pro Thr Ala Ala Lys Tyr Glu Tyr Gly Val Pro Leu Gln Thr Ser Asp  
   130                      135                      140  
  
 Ser Phe Leu Arg Phe Pro Ser Ser Leu Thr Ser Ser Leu Cys Thr Asp  
   145                      150                      155                      160  
  
 Asn Asn Pro Ala Ala Phe Leu Val Asn Gln Ala Val Lys Cys Thr Arg  
                     165                      170                      175  
  
 Lys Ile Asn Leu Glu Gln Cys Glu Glu Ile Glu Ala Leu Ser Met Ala  
   180                      185                      190  
  
 Phe Tyr Ser Ser Pro Glu Ile Leu Arg Val Pro Asp Ser Arg Lys Lys  
   195                      200                      205  
  
 Val Pro Ile Thr Val Gln Ser Ile Val Ile Gln Ser Leu Asn Lys Thr  
   210                      215                      220  
  
 Leu Thr Arg Arg Glu Asp Thr Asp Val Leu Gln Pro Thr Leu Val Asn  
   225                      230                      235                      240  
  
 Ala Gly His Phe Ser Leu Cys Val Asn Val Val Leu Glu Val Lys Tyr  
                     245                      250                      255  
  
 Ser Leu Thr Tyr Thr Asp Ala Gly Glu Val Thr Lys Ala Asp Leu Ser

235

260	265	270
Phe Val Leu Gly Thr Val Ser	Ser Val Val Val Pro	Leu Gln Gln Lys
275	280	285
Phe Glu Ile His Phe Leu Gln	Glu Asn Thr Gln Pro	Val Pro Leu Ser
290	295	300
Gly Asn Pro Gly Tyr Val	Val Gly Leu Pro	Leu Ala Ala
305	310	315

&lt;210&gt; 419

&lt;211&gt; 118

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (9)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (91)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 419

Cys	Leu	Leu	His	Pro	Ile	Ile	Pro	Xaa	Pro	Val	Ile	Asn	Gly	Tyr	Arg
1				5					10					15	

Asn	Lys	Ser	Thr	Phe	Ser	Val	Asn	Arg	Gly	Pro	Asp	Gly	Asn	Pro	Lys
			20					25					30		

Thr	Val	Gly	Phe	Tyr	Leu	Gly	Thr	Trp	Arg	Asp	Gly	Asn	Val	Val	Cys
		35					40					45			

Val	Gln	Ser	Asn	His	Leu	Lys	Asn	Ile	Pro	Glu	Lys	His	Ser	Gln	Val
	50					55					60				

Ala	Gln	Tyr	Tyr	Glu	Val	Phe	Leu	Arg	Gln	Ser	Pro	Leu	Glu	Pro	Cys
65					70					75					80

Leu	Val	Phe	His	Glu	Gly	Gly	Tyr	Trp	Arg	Xaa	Leu	Thr	Val	Arg	Thr
				85					90					95	

Asn	Ser	Gln	Gly	His	Thr	Met	Ala	Ile	Ile	Thr	Phe	His	Pro	Gln	Lys
			100					105					110		

Leu	Ser	Gln	Glu	Glu	Leu
		115			

&lt;210&gt; 420

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 420

Gly	Pro	Gly	Ala	Ala	Cys	Gly	Leu	Thr	Ser	Leu	Tyr	Phe	Gln	Glu
1				5					10					15

&lt;210&gt; 421

&lt;211&gt; 54

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 421

236

Gly Trp Gln Ala Leu Arg Glu Glu Ser His Cys Thr Ala Ser Asp Thr  
 1 5 10 15  
 Ser Ser Pro Trp Trp Val Ser Ser Pro Asn Gln Asp Cys Phe Pro Gly  
 20 25 30  
 Met Pro Glu Ile His Gln Asp Gly His Ser Ser Phe Trp Ala Gln Tyr  
 35 40 45  
 Val Arg Glu Ile Ser Pro  
 50

<210> 422  
 <211> 191  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (130)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 422  
 Asn Cys Gln Glu Met Ser Asn Thr Asn Gly Ser Ala Ile Thr Glu Phe  
 1 5 10 15  
 Ile Leu Leu Gly Leu Thr Asp Cys Pro Glu Leu Gln Ser Leu Leu Phe  
 20 25 30  
 Val Leu Phe Leu Val Val Tyr Leu Val Thr Leu Leu Gly Asn Leu Gly  
 35 40 45  
 Met Ile Met Leu Met Arg Leu Asp Ser Arg Leu His Thr Pro Met Tyr  
 50 55 60  
 Phe Phe Leu Thr Asn Leu Ala Phe Val Asp Leu Cys Tyr Thr Ser Asn  
 65 70 75 80  
 Ala Thr Pro Gln Met Ser Thr Asn Ile Val Ser Glu Lys Thr Ile Ser  
 85 90 95  
 Phe Ala Gly Cys Phe Thr Gln Cys Tyr Ile Phe Ile Ala Leu Leu Leu  
 100 105 110  
 Thr Glu Phe Tyr Met Leu Ala Ala Met Ala Tyr Asp Arg Tyr Val Ala  
 115 120 125  
 Ile Xaa Asp Pro Leu Arg Tyr Ser Val Lys Thr Ser Arg Arg Val Cys  
 130 135 140  
 Ile Cys Leu Ala Thr Phe Pro Tyr Val Tyr Gly Phe Ser Asp Gly Leu  
 145 150 155 160  
 Phe Gln Ala Ile Leu Thr Phe Arg Leu Thr Phe Cys Arg Ser Asn Val  
 165 170 175  
 Ile Asn His Phe Tyr Cys Ala Asp Pro Pro Leu Ile Lys Leu Ser  
 180 185 190

<210> 423  
 <211> 110  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE

237

&lt;222&gt; (65)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (90)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (97)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (103)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 423

Asp	Ile	Cys	Gly	Ser	Arg	Asn	Ser	Cys	Val	Ser	Cys	Val	Asp	Gly	Asn
1				5					10					15	

Ala	Thr	Cys	Phe	Trp	Ile	Glu	Cys	Lys	Gly	Lys	Ser	Tyr	Cys	Ser	Asp
			20					25					30		

Asn	Ser	Thr	Ala	Gly	Asp	Cys	Lys	Val	Val	Asn	Thr	Thr	Gly	Phe	Cys
		35					40					45			

Ser	Ala	Lys	Thr	Thr	Thr	Leu	Pro	Ser	Thr	Thr	Thr	Thr	Ser	Thr	Thr
	50					55					60				

Xaa	Thr	Thr	Ser	Gly	Thr	Thr	Asn	Thr	Thr	Leu	Ser	Pro	Thr	Ile	Gln
65					70					75				80	

Pro	Thr	Arg	Lys	Ser	Thr	Phe	Asp	Ala	Xaa	Gln	Phe	His	Trp	Arg	Asn
			85						90					95	

Xaa	Pro	Cys	Leu	Gly	Val	Xaa	Ala	Val	Ile	Phe	Phe	Leu	Tyr
		100						105					110

&lt;210&gt; 424

&lt;211&gt; 146

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 424

Leu	Lys	Lys	Thr	Trp	Ala	Arg	Trp	Arg	His	Met	Phe	Arg	Glu	Gln	Pro
1				5					10					15	

Val	Asp	Glu	Ile	Arg	Asn	Tyr	Phe	Gly	Glu	Lys	Val	Ala	Leu	Tyr	Phe
			20					25					30		

Val	Trp	Leu	Gly	Trp	Tyr	Thr	Tyr	Met	Leu	Val	Pro	Ala	Ala	Leu	Thr
		35					40					45			

Gly	Leu	Leu	Val	Phe	Leu	Ser	Gly	Phe	Ser	Leu	Phe	Glu	Ala	Ser	Gln
	50					55					60				

Ile	Ser	Lys	Glu	Ile	Cys	Glu	Ala	His	Asp	Ile	Leu	Met	Cys	Pro	Leu
65					70					75				80	

Gly	Asp	His	Ser	Arg	Arg	Tyr	Gln	Arg	Leu	Ser	Glu	Thr	Cys	Thr	Phe
				85					90					95	

Ala	Lys	Leu	Thr	His	Leu	Phe	Asp	Asn	Asp	Gly	Thr	Val	Val	Phe	Ala
			100					105					110		

238

Ile Phe Met Ala Leu Trp Ala Thr Val Phe Leu Glu Ile Trp Lys Arg  
 115 120 125

Gln Arg Ala Arg Val Val Leu His Trp Asp Leu Tyr Val Trp Asp Glu  
 130 135 140

Glu Gln  
 145

<210> 425

<211> 44

<212> PRT

<213> Homo sapiens

<400> 425

Met Glu Ser Arg Ser Val Ser Gln Ala Gly Gly Gln Trp Arg Asp Leu  
 1 5 10 15

Gly Ser Leu Gln Pro Pro Pro Pro Arg Phe Lys Arg Phe Ser Cys Leu  
 20 25 30

Gly Leu Pro Lys Cys Trp Asp Tyr Arg His Glu Pro  
 35 40

<210> 426

<211> 40

<212> PRT

<213> Homo sapiens

<400> 426

Ser Val Ser Gln Ala Gly Gly Gln Trp Arg Asp Leu Gly Ser Leu Gln  
 1 5 10 15

Pro Pro Pro Pro Arg Phe Lys Arg Phe Ser Cys Leu Gly Leu Pro Lys  
 20 25 30

Cys Trp Asp Tyr Arg His Glu Pro  
 35 40

<210> 427

<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (39)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 427

Pro Arg Leu Lys Gln Ser Phe Cys Leu Asp Leu Pro Arg Cys Trp Asp  
 1 5 10 15

Tyr Arg His Glu Pro Leu His Leu Ala Phe Ile Xaa Phe Leu Ser Phe  
 20 25 30

Phe Leu Ser Phe Phe Phe Xaa Met Glu Ser Arg Ser Val Ser Gln Ala  
 35 40 45

Gly Gly Gln Trp Arg Asp Leu Gly Ser Leu Gln Pro Pro Pro Pro Arg

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50                               55                               60
Phe Lys
65

<210> 428
<211> 44
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (7)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 428
Ala Gln Ala Gly Val Gln Xaa Leu Asn Leu Ser Ser Leu Gln Pro Gln
 1                               5                               10                               15
Pro Ala Gly Leu Lys Gln Ser Ser His Pro Ser Leu Pro Ser Ser Trp
                20                               25                               30
Asp Tyr Arg Tyr Ser Thr Pro His Pro Ala Asn Phe
                35                               40

<210> 429
<211> 31
<212> PRT
<213> Homo sapiens

<400> 429
Phe Phe Cys Arg Asp Gly Ile Ser Pro Cys Cys Pro Gly Trp Ser Arg
 1                               5                               10                               15
Thr Pro Arg Leu Arg Arg Ser Ala His Leu Asn Leu Pro Gln Cys
                20                               25                               30

<210> 430
<211> 356
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (189)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (253)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 430
Met Phe Gly Thr Leu Leu Leu Tyr Cys Phe Phe Leu Ala Thr Val Pro
 1                               5                               10                               15
Ala Leu Ala Glu Thr Gly Gly Glu Arg Gln Leu Ser Pro Glu Lys Ser
                20                               25                               30
Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu Pro Ala Arg
                35                               40                               45
Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn Lys Phe Thr Ser
 50                               55                               60
Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val Ser Ala Pro Glu Glu

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240

65					70					75					80
Gln	Phe	Thr	Arg	Val	Gly	Val	Gln	Val	Leu	Asp	Arg	Lys	Asp	Gly	Ser
				85					90					95	
Phe	Ile	Val	Arg	Tyr	Arg	Met	Tyr	Ala	Ser	Tyr	Lys	Asn	Leu	Lys	Val
			100					105					110		
Glu	Val	Lys	Phe	Gln	Gly	Gln	His	Val	Ala	Lys	Ser	Pro	Tyr	Ile	Leu
		115					120					125			
Lys	Gly	Pro	Val	Tyr	His	Glu	Asn	Cys	Asp	Cys	Pro	Leu	Gln	Asp	Ser
	130					135					140				
Ala	Ala	Trp	Leu	Arg	Glu	Met	Asn	Cys	Pro	Glu	Thr	Ile	Ala	Gln	Ile
145					150					155					160
Gln	Arg	Asp	Leu	Ala	His	Phe	Pro	Ala	Val	Asp	Pro	Glu	Lys	Ile	Ala
				165					170					175	
Val	Glu	Ile	Pro	Lys	Arg	Phe	Gly	Gln	Arg	Gln	Ser	Xaa	Cys	His	Tyr
			180					185					190		
Thr	Leu	Lys	Asp	Asn	Lys	Val	Tyr	Ile	Lys	Thr	His	Gly	Glu	His	Val
		195					200					205			
Gly	Phe	Arg	Ile	Phe	Met	Asp	Ala	Ile	Leu	Leu	Ser	Leu	Thr	Arg	Lys
	210					215					220				
Val	Lys	Met	Pro	Asp	Val	Glu	Leu	Phe	Val	Asn	Leu	Gly	Asp	Trp	Pro
225					230					235					240
Leu	Glu	Lys	Lys	Lys	Ser	Asn	Ser	Asn	Ile	His	Pro	Xaa	Phe	Ser	Trp
				245					250					255	
Cys	Gly	Ser	Thr	Asp	Ser	Lys	Asp	Ile	Val	Met	Pro	Thr	Tyr	Asp	Leu
			260					265					270		
Thr	Asp	Ser	Val	Leu	Glu	Thr	Met	Gly	Arg	Val	Ser	Leu	Asp	Met	Met
		275					280					285			
Ser	Val	Gln	Ala	Asn	Thr	Gly	Pro	Pro	Trp	Glu	Ser	Lys	Asn	Ser	Thr
	290					295					300				
Ala	Val	Trp	Arg	Gly	Arg	Asp	Ser	Arg	Lys	Glu	Arg	Leu	Glu	Leu	Val
305					310					315					320
Lys	Leu	Ser	Arg	Lys	His	Pro	Glu	Leu	Ile	Asp	Ala	Ala	Phe	Thr	Asn
				325					330					335	
Phe	Phe	Phe	Phe	Lys	His	Asp	Glu	Asn	Leu	Tyr	Gly	Pro	Ile	Val	Asn
			340					345					350		
Ile	Phe	His	Phe												
			355												

&lt;210&gt; 431

&lt;211&gt; 151

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (14)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids



241

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (70)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 431

Glu His Ile Ser Phe Phe Asp Phe Phe Lys His Lys Tyr Xaa Ile Asn  
 1 5 10 15

Ile Asp Gly Thr Val Ala Ala Tyr Arg Leu Pro Tyr Leu Leu Val Gly  
 20 25 30

Asp Ser Val Val Leu Lys Gln Asp Ser Ile Tyr Tyr Glu His Phe Tyr  
 35 40 45

Asn Glu Leu Gln Pro Trp Lys His Tyr Ile Pro Val Lys Ser Asn Leu  
 50 55 60

Ser Asp Leu Leu Glu Xaa Leu Lys Trp Ala Lys Asp His Asp Glu Glu  
 65 70 75 80

Ala Lys Lys Ile Ala Lys Ala Gly Gln Glu Phe Ala Arg Asn Asn Leu  
 85 90 95

Met Gly Asp Asp Ile Phe Cys Tyr Tyr Phe Lys Leu Phe Gln Glu Tyr  
 100 105 110

Ala Asn Leu Gln Val Ser Glu Pro Gln Ile Arg Glu Gly Met Lys Arg  
 115 120 125

Val Glu Pro Gln Thr Glu Asp Asp Leu Phe Pro Cys Thr Cys His Arg  
 130 135 140

Lys Lys Thr Lys Asp Glu Leu  
 145 150

&lt;210&gt; 432

&lt;211&gt; 158

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 432

Asp Trp Leu Thr Glu Lys Pro Glu Leu Phe Gln Leu Ala Leu Lys Ala  
 1 5 10 15

Phe Arg Tyr Thr Leu Lys Leu Met Ile Asp Lys Ala Ser Leu Gly Pro  
 20 25 30

Ile Glu Asp Phe Arg Glu Leu Ile Lys Tyr Leu Glu Glu Tyr Glu Arg  
 35 40 45

Asp Trp Tyr Ile Gly Leu Val Ser Asp Glu Lys Trp Lys Glu Ala Ile  
 50 55 60

Leu Gln Glu Lys Pro Tyr Leu Phe Ser Leu Gly Tyr Asp Ser Asn Met  
 65 70 75 80

Gly Ile Tyr Thr Gly Arg Val Leu Ser Leu Gln Glu Leu Leu Ile Gln  
 85 90 95

Val Gly Lys Leu Asn Pro Glu Ala Val Arg Gly Gln Trp Ala Asn Leu  
 100 105 110

Ser Trp Glu Leu Leu Tyr Ala Thr Asn Asp Asp Glu Glu Arg Tyr Ser  
 115 120 125

242

Ile Gln Ala His Pro Leu Leu Leu Arg Asn Leu Thr Val Gln Ala Ala  
 130 135 140

Glu Pro Pro Leu Gly Tyr Pro Ile Tyr Ser Ser Lys Pro Leu  
 145 150 155

<210> 433

<211> 120

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (64)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 433

Val Arg Met Glu Met Ala Ser Ser Ala Gly Ser Trp Leu Ser Gly Cys  
 1 5 10 15

Leu Ile Pro Leu Val Phe Leu Arg Leu Ser Val His Val Ser Gly His  
 20 25 30

Ala Gly Asp Ala Gly Lys Phe His Val Ala Leu Leu Gly Gly Thr Ala  
 35 40 45

Glu Leu Leu Cys Pro Leu Ser Leu Trp Pro Gly Thr Val Pro Lys Xaa  
 50 55 60

Val Arg Trp Leu Arg Ser Pro Phe Pro Gln Arg Ser Gln Ala Val His  
 65 70 75 80

Ile Phe Arg Asp Gly Lys Asp Gln Asp Glu Asp Leu Met Pro Glu Tyr  
 85 90 95

Lys Gly Arg Thr Val Leu Val Arg Asp Ala Gln Glu Gly Ser Val Thr  
 100 105 110

Leu Gln Ile Leu Asp Val Arg Leu  
 115 120

<210> 434

<211> 143

<212> PRT

<213> Homo sapiens

<400> 434

Asp Pro His Gln Leu Phe Asp Asp Thr Ser Ser Ala Gln Ser Arg Gly  
 1 5 10 15

Tyr Gly Ala Gln Arg Ala Pro Gly Gly Leu Ser Tyr Pro Ala Ala Ser  
 20 25 30

Pro Thr Pro His Ala Ala Phe Leu Ala Asp Pro Val Ser Asn Met Ala  
 35 40 45

Met Ala Tyr Gly Ser Ser Leu Ala Ala Gln Gly Lys Glu Leu Val Asp  
 50 55 60

Lys Asn Ile Asp Arg Phe Ile Pro Ile Thr Lys Leu Lys Tyr Tyr Phe  
 65 70 75 80

Ala Val Asp Thr Met Tyr Val Gly Arg Lys Leu Gly Leu Leu Phe Phe  
 85 90 95

Pro Tyr Leu His Gln Asp Trp Glu Val Gln Tyr Gln Gln Asp Thr Pro

243

	100		105		110										
Val	Ala	Pro	Arg	Phe	Asp	Val	Asn	Ala	Pro	Asp	Leu	Tyr	Ile	Pro	Ala
	115						120					125			
Met	Ala	Phe	Ile	Thr	Tyr	Val	Leu	Val	Ala	Gly	Leu	Arg	Trp	Gly	
	130						135				140				

&lt;210&gt; 435

&lt;211&gt; 179

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (102)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (160)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 435

Met	Asn	Met	Ser	Val	Leu	Thr	Leu	Gln	Glu	Tyr	Glu	Phe	Glu	Lys	Gln
1				5					10					15	

Phe	Asn	Glu	Asn	Glu	Ala	Ile	Gln	Trp	Met	Gln	Glu	Asn	Trp	Lys	Lys
			20					25					30		

Ser	Phe	Leu	Phe	Ser	Ala	Leu	Tyr	Ala	Ala	Phe	Ile	Phe	Gly	Gly	Arg
		35					40					45			

His	Leu	Met	Asn	Lys	Arg	Ala	Lys	Phe	Glu	Leu	Arg	Lys	Pro	Leu	Val
	50					55					60				

Leu	Trp	Ser	Leu	Thr	Leu	Ala	Val	Phe	Ser	Ile	Phe	Gly	Ala	Leu	Arg
65					70					75					80

Thr	Gly	Ala	Tyr	Met	Val	Tyr	Ile	Leu	Met	Thr	Lys	Gly	Leu	Lys	Gln
				85					90					95	

Ser	Val	Cys	Asp	Gln	Xaa	Phe	Tyr	Asn	Gly	Pro	Val	Ser	Lys	Phe	Trp
			100					105					110		

Ala	Tyr	Ala	Phe	Val	Leu	Ser	Lys	Ala	Pro	Glu	Leu	Gly	Asp	Thr	Ile
		115					120					125			

Phe	Ile	Ile	Leu	Arg	Lys	Gln	Lys	Leu	Ile	Phe	Leu	His	Trp	Tyr	His
	130					135					140				

His	Ile	Thr	Val	Leu	Leu	Tyr	Ser	Trp	Tyr	Ser	Tyr	Lys	Asp	Met	Xaa
145					150					155					160

Cys	Arg	Gly	Gly	Trp	Phe	Met	Thr	Met	Asn	Tyr	Gly	Val	His	Ala	Val
				165					170					175	

Met Tyr Ser

&lt;210&gt; 436

&lt;211&gt; 98

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 436

244

Arg Trp Asn Phe Ser Leu Ile Ala Gln Ala Gly Val Gln Trp His Asp  
 1 5 10 15  
 Leu Gly Ser Pro Gln Pro Pro Pro Pro Gly Leu Lys Arg Phe Ser Phe  
 20 25 30  
 Leu Gly Leu Pro Ser Ser Trp Asp Tyr Arg His Ala Pro Pro Cys Pro  
 35 40 45  
 Ala Asn Phe Val Phe Leu Val Glu Met Gly Phe Leu His Val Gly Gln  
 50 55 60  
 Ala Gly Leu Glu Leu Pro Thr Ser Gly Gly Pro Pro Ala Trp Ala Ser  
 65 70 75 80  
 Gln Ser Ala Gly Ile Thr Gly Val Ser His Arg Ala Trp Pro Glu Asn  
 85 90 95  
 Ser His

<210> 437  
 <211> 583  
 <212> PRT  
 <213> Homo sapiens

<400> 437  
 Val Thr Arg Gln Asp Met Asn Asp Ala Val Ile Thr Leu Asn Gly Leu  
 1 5 10 15  
 Glu Lys Arg Phe Pro Gly Met Asp Lys Pro Ala Val Ala Pro Leu Asp  
 20 25 30  
 Cys Thr Ile His Ala Gly Tyr Val Thr Gly Leu Val Gly Pro Asp Gly  
 35 40 45  
 Ala Gly Lys Thr Thr Leu Met Arg Met Leu Ala Gly Leu Leu Lys Pro  
 50 55 60  
 Asp Ser Gly Ser Ala Thr Val Ile Gly Phe Asp Pro Ile Lys Asn Asp  
 65 70 75 80  
 Gly Ala Leu His Ala Val Leu Gly Tyr Met Pro Gln Lys Phe Gly Leu  
 85 90 95  
 Tyr Glu Asp Leu Thr Val Met Glu Asn Leu Asn Leu Tyr Ala Asp Leu  
 100 105 110  
 Arg Ser Val Thr Gly Glu Ala Arg Lys Gln Thr Phe Ala Arg Leu Leu  
 115 120 125  
 Glu Phe Thr Ser Leu Gly Pro Phe Thr Gly Arg Leu Ala Gly Lys Leu  
 130 135 140  
 Ser Gly Gly Met Lys Gln Lys Leu Gly Leu Ala Cys Thr Leu Val Gly  
 145 150 155 160  
 Glu Pro Lys Val Leu Leu Leu Asp Glu Pro Gly Val Gly Val Asp Pro  
 165 170 175  
 Ile Ser Arg Arg Glu Leu Trp Gln Met Val His Glu Leu Ala Gly Glu  
 180 185 190  
 Gly Met Leu Ile Leu Trp Ser Thr Ser Tyr Leu Asp Glu Ala Glu Gln  
 195 200 205

Cys 210	Arg	Asp	Val	Leu	Leu	Met 215	Asn	Glu	Gly	Glu	Leu 220	Leu	Tyr	Gln	Gly
Glu 225	Pro	Lys	Ala	Leu	Thr 230	Gln	Thr	Met	Ala	Gly 235	Arg	Ser	Phe	Leu	Met 240
Thr	Ser	Pro	His	Glu 245	Gly	Asn	Arg	Lys	Leu 250	Leu	Gln	Arg	Ala	Leu 255	Lys
Leu	Pro	Gln	Val 260	Ser	Asp	Gly	Met	Ile 265	Gln	Gly	Lys	Ser	Val 270	Arg	Leu
Ile	Leu	Lys 275	Lys	Glu	Ala	Thr	Pro 280	Asp	Asp	Ile	Arg	His 285	Ala	Asp	Gly
Met	Pro 290	Glu	Ile	Asn	Ile	Asn 295	Glu	Thr	Thr	Pro	Arg 300	Phe	Glu	Asp	Ala
Phe 305	Ile	Asp	Leu	Leu	Gly 310	Gly	Ala	Gly	Thr	Ser 315	Glu	Ser	Pro	Leu	Gly 320
Ala	Ile	Leu	His	Thr 325	Val	Glu	Gly	Thr	Pro 330	Gly	Glu	Thr	Val	Ile 335	Glu
Ala	Lys	Glu	Leu 340	Thr	Lys	Lys	Phe	Gly 345	Asp	Phe	Ala	Ala	Thr 350	Asp	His
Val	Asn	Phe 355	Ala	Val	Lys	Arg	Gly 360	Glu	Ile	Phe	Gly	Leu 365	Leu	Gly	Pro
Asn	Gly 370	Ala	Gly	Lys	Ser	Thr 375	Thr	Phe	Lys	Met	Met 380	Cys	Gly	Leu	Leu
Val 385	Pro	Thr	Ser	Gly	Gln 390	Ala	Leu	Val	Leu	Gly 395	Met	Asp	Leu	Lys	Glu 400
Ser	Ser	Gly	Lys	Ala 405	Arg	Gln	His	Leu	Gly 410	Tyr	Met	Ala	Gln	Lys 415	Phe
Ser	Leu	Tyr	Gly 420	Asn	Leu	Thr	Val	Glu 425	Gln	Asn	Leu	Arg	Phe 430	Phe	Ser
Gly	Val	Tyr 435	Gly	Leu	Arg	Gly	Arg 440	Ala	Gln	Asn	Glu	Lys 445	Ile	Ser	Arg
Met	Ser 450	Glu	Ala	Phe	Gly	Leu 455	Lys	Ser	Ile	Ala	Ser 460	His	Ala	Thr	Asp
Glu 465	Leu	Pro	Leu	Gly	Phe 470	Lys	Gln	Arg	Leu	Ala 475	Leu	Ala	Cys	Ser	Leu 480
Met	His	Glu	Pro	Asp 485	Ile	Leu	Phe	Leu	Asp 490	Glu	Pro	Thr	Ser	Gly 495	Val
Asp	Pro	Leu	Thr 500	Arg	Arg	Glu	Phe	Trp 505	Leu	His	Ile	Asn	Ser 510	Met	Val
Glu	Lys	Gly 515	Val	Thr	Val	Met	Val 520	Thr	Thr	His	Phe	Met 525	Asp	Glu	Ala
Glu	Tyr 530	Cys	Asp	Arg	Ile	Gly 535	Leu	Val	Tyr	Arg	Gly 540	Lys	Leu	Ile	Ala
Ser 545	Gly	Thr	Pro	Asp	Asp 550	Leu	Lys	Ala	Gln	Ser 555	Ala	Asn	Asp	Glu	Gln 560

246

Pro Asp Pro Thr Met Glu Gln Ala Phe Ile Gln Leu Ile His Asp Trp  
                                   565                                  570                                  575

Asp Lys Glu His Ser Asn Glu  
                                   580

&lt;210&gt; 438

&lt;211&gt; 72

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 438

Ser Ile Glu Leu Leu Gly Ser Asp Asp Leu Ser Thr Ser Ala Ser Gln  
   1                                  5                                  10                                  15

Val Val Gly Thr Leu Gly Met Leu Cys His Ala Trp Leu Leu Leu Met  
                                   20                                  25                                  30

Tyr Leu Phe Leu Glu Met Arg Ser His Cys Val Ala Gln Thr Gly Leu  
                                   35                                  40                                  45

Glu Leu Leu Ala Ser Ser His Pro Pro Phe Ser Ala Ser Thr Val Ala  
   50                                  55                                  60

Gly Ile Ser Gly Thr Cys His Cys  
   65                                  70

&lt;210&gt; 439

&lt;211&gt; 143

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 439

Asp Pro His Gln Leu Phe Asp Asp Thr Ser Ser Ala Gln Ser Arg Gly  
   1                                  5                                  10                                  15

Tyr Gly Ala Gln Arg Ala Pro Gly Gly Leu Ser Tyr Pro Ala Ala Ser  
                                   20                                  25                                  30

Pro Thr Pro His Ala Ala Phe Leu Ala Asp Pro Val Ser Asn Met Ala  
                                   35                                  40                                  45

Met Ala Tyr Gly Ser Ser Leu Ala Ala Gln Gly Lys Glu Leu Val Asp  
   50                                  55                                  60

Lys Asn Ile Asp Arg Phe Ile Pro Ile Thr Lys Leu Lys Tyr Tyr Phe  
   65                                  70                                  75                                  80

Ala Val Asp Thr Met Tyr Val Gly Arg Lys Leu Gly Leu Leu Phe Phe  
                                   85                                  90                                  95

Pro Tyr Leu His Gln Asp Trp Glu Val Gln Tyr Gln Gln Asp Thr Pro  
                                   100                                  105                                  110

Val Ala Pro Arg Phe Asp Val Asn Ala Pro Asp Leu Tyr Ile Pro Ala  
                                   115                                  120                                  125

Met Ala Phe Ile Thr Tyr Val Leu Val Ala Gly Leu Arg Trp Gly  
   130                                  135                                  140

&lt;210&gt; 440

&lt;211&gt; 234

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

247

<221> SITE  
 <222> (10)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (93)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (95)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (101)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 440  
 Gly Pro Ala Pro Cys Pro Thr Leu Gly Xaa Ser Cys Cys Cys Ser Cys  
   1                  5                  10                  15  
 Cys Cys Cys Pro Ser Gly Ala Lys Pro Thr Gln Ala Ala Thr Gly Ser  
                   20                  25                  30  
 Gln Gly Cys Pro Ala Cys Pro Gly His Gln Gly Arg Met Gly Thr Thr  
           35                  40                  45  
 Asp Cys Arg Gly Pro Arg Gly Ser Gln Glu Ser Gln Pro Phe Pro Gly  
   50                  55                  60  
 Ser Glu Asp Pro Lys Gly Arg Arg Glu Asn Pro Ala Tyr Pro Ala Ile  
   65                  70                  75                  80  
 Leu Gly Lys Met Ala Pro Trp Asp Pro Leu Gly Cys Xaa Gly Xaa Pro  
                   85                  90                  95  
 Ala Pro Trp Ala Xaa Leu Glu Ser Gln Lys Phe Gln Ser Val Phe Thr  
                   100                  105                  110  
 Val Thr Arg Gln Thr His Gln Pro Pro Ala Pro Asn Ser Leu Ile Arg  
   115                  120                  125  
 Phe Asn Ala Val Leu Thr Asn Pro Gln Gly Asp Tyr Asp Thr Ser Thr  
   130                  135                  140  
 Gly Lys Phe Thr Cys Lys Val Pro Gly Leu Tyr Tyr Phe Val Tyr His  
   145                  150                  155                  160  
 Ala Ser His Thr Ala Asn Leu Cys Val Leu Leu Tyr Arg Ser Gly Val  
                   165                  170                  175  
 Lys Val Val Thr Phe Cys Gly His Thr Ser Lys Thr Asn Gln Val Asn  
                   180                  185                  190  
 Ser Gly Gly Val Leu Leu Arg Leu Gln Val Gly Glu Glu Val Trp Leu  
   195                  200                  205  
 Ala Val Asn Asp Tyr Tyr Asp Met Val Gly Ile Gln Gly Ser Asp Ser  
   210                  215                  220  
 Val Phe Ser Gly Phe Leu Leu Phe Pro Asp  
   225                  230  
  
 <210> 441

248

<211> 97  
 <212> PRT  
 <213> Homo sapiens

<400> 441  
 Gly Phe Thr Leu Trp Gly Ser Glu Tyr Ser Trp Asn Trp Asn Ala Ile  
     1                    5                    10                    15  
 Asp Glu Gly Pro Lys Arg Asp Ile Val Lys Glu Leu Glu Val Ala Ile  
                     20                    25                    30  
 Arg Asn Arg Thr Asp Leu Arg Phe Gly Leu Tyr Tyr Ser Leu Phe Glu  
                     35                    40                    45  
 Trp Phe His Pro Leu Phe Leu Glu Asp Glu Ser Ser Ser Phe His Lys  
     50                    55                    60  
 Arg Gln Phe Pro Val Ser Lys Thr Leu Pro Glu Leu Tyr Glu Leu Val  
     65                    70                    75                    80  
 Asn Asn Tyr Gln Pro Glu Val Leu Trp Ser Asp Gly Asp Gly Gly Glu  
                     85                    90                    95  
 Pro

<210> 442  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 442  
 Ala His Ser Ala Thr Arg Phe Asp Pro Thr Trp Glu Ser Leu Asp Ala  
     1                    5                    10                    15  
 Arg Gln Leu Pro Ala Trp Phe Asp Gln Ala Lys Phe Gly Ile Phe Ile  
                     20                    25                    30  
 His Trp Gly Val Phe Ser Val Pro Ser Phe Gly Ser Glu Trp Phe Trp  
                     35                    40                    45  
 Leu Tyr  
     50

<210> 443  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 443  
 Tyr Trp Asn Ser Thr Gly Phe Leu Ala Trp Leu Tyr Asn Glu Ser Pro  
     1                    5                    10                    15  
 Val Arg Gly Thr Val Val Thr Asn Asp Arg Trp Gly  
                     20                    25

<210> 444  
 <211> 309  
 <212> PRT  
 <213> Homo sapiens

<400> 444  
 Phe His Phe Thr Asp Cys Leu Phe Phe Gly Ser Leu Met Ser Ala Thr  
     1                    5                    10                    15  
 Asp Pro Val Thr Val Leu Ala Ile Phe His Glu Leu His Val Asp Pro



249

20					25					30					
Asp	Leu	Tyr <sub>35</sub>	Thr	Leu	Leu	Phe	Gly <sub>40</sub>	Glu	Ser	Val	Leu	Asn <sub>45</sub>	Asp	Ala	Val
Ala	Ile	Val <sub>50</sub>	Leu	Thr	Tyr	Ser <sub>55</sub>	Ile	Ser	Ile	Tyr	Ser <sub>60</sub>	Pro	Lys	Glu	Asn
Pro	Asn	Ala	Phe	Asp	Ala <sub>70</sub>	Ala	Ala	Phe	Phe	Gln <sub>75</sub>	Ser	Val	Gly	Asn	Phe <sub>80</sub>
Leu	Gly	Ile	Phe	Ala	Gly <sub>85</sub>	Ser	Phe	Ala	Met	Gly <sub>90</sub>	Ser	Ala	Tyr	Ala	Ile <sub>95</sub>
Ile	Thr	Ala	Leu	Leu	Thr	Lys	Phe	Thr <sub>105</sub>	Lys	Leu	Cys	Glu	Phe	Pro	Met <sub>110</sub>
Leu	Glu	Thr <sub>115</sub>	Gly	Leu	Phe	Phe	Leu	Leu	Ser	Trp	Ser	Ala <sub>125</sub>	Phe	Leu	Ser
Ala	Glu	Ala	Ala	Gly	Leu	Thr <sub>135</sub>	Gly	Ile	Val	Ala	Val <sub>140</sub>	Leu	Phe	Cys	Gly
Val	Thr	Gln	Ala	His	Tyr <sub>150</sub>	Thr	Tyr	Asn	Asn	Leu <sub>155</sub>	Ser	Ser	Asp	Ser	Lys <sub>160</sub>
Ile	Arg	Thr	Lys	Gln	Leu <sub>165</sub>	Phe	Glu	Phe	Met	Asn <sub>170</sub>	Phe	Leu	Ala	Glu	Asn <sub>175</sub>
Val	Ile	Phe	Cys	Tyr	Met	Gly	Leu	Ala <sub>185</sub>	Leu	Phe	Thr	Phe	Gln <sub>190</sub>	Asn	His
Ile	Phe	Asn <sub>195</sub>	Ala	Leu	Phe	Ile	Leu	Gly <sub>200</sub>	Ala	Phe	Leu	Ala <sub>205</sub>	Ile	Phe	Val
Ala	Arg	Ala	Cys	Asn	Ile	Tyr <sub>215</sub>	Pro	Leu	Ser	Phe	Leu	Leu	Asn	Leu	Gly
Arg	Lys	Gln	Lys	Ile	Pro <sub>230</sub>	Trp	Asn	Phe	Gln	His <sub>235</sub>	Met	Met	Met	Phe	Ser <sub>240</sub>
Gly	Leu	Arg	Gly	Ala	Ile <sub>245</sub>	Ala	Phe	Ala	Leu	Ala <sub>250</sub>	Ile	Arg	Asn	Thr	Glu <sub>255</sub>
Ser	Gln	Pro	Lys	Gln	Met	Met	Phe	Thr <sub>265</sub>	Thr	Thr	Leu	Leu	Leu	Val	Phe <sub>270</sub>
Phe	Thr	Val <sub>275</sub>	Trp	Val	Phe	Gly	Gly <sub>280</sub>	Gly	Thr	Thr	Pro	Met <sub>285</sub>	Leu	Thr	Trp
Leu	Gln	Ile	Arg	Val	Gly <sub>295</sub>	Val	Asp	Leu	Asp	Glu	Asn <sub>300</sub>	Leu	Lys	Glu	Asp
Pro Ser Ser Gln His															
305															

&lt;210&gt; 445

&lt;211&gt; 94

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

250

&lt;400&gt; 445

Ser	Met	Glu	Val	Gly	Val	Cys	Val	Glu	Ala	Tyr	Arg	Gln	Glu	Ala	Glu
1				5					10					15	
Thr	His	Arg	Arg	His	Xaa	Asn	Ser	Ala	Phe	Met	Thr	Phe	Val	Val	Leu
			20					25					30		
Asp	Ala	Asp	Asp	Gln	Pro	Gln	Leu	Leu	Pro	Trp	Ile	Arg	Pro	Gln	Pro
		35					40					45			
Gly	Asp	Gly	Glu	Arg	Arg	Tyr	Arg	Glu	Ala	Ser	Ala	Arg	Lys	Lys	Ile
	50					55					60				
Arg	Leu	Asp	Arg	Lys	Tyr	Ile	Val	Ser	Cys	Lys	Gln	Thr	Glu	Val	Pro
65					70					75					80
Leu	Ser	Val	Pro	Trp	Asp	Pro	Ser	Asn	Gln	Val	Tyr	Leu	Ser		
				85					90						

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/05064

### Box I - Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claim 23 is directed to a product of the method of claim 20. Claim 20 is not a method for the production of a product, but a process for the detection for the detection of a substance. Hence, no meaningful search can be carried out.
2. ☐ Claim Nos.: 23  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐  
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/05064

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/11, 15/12, 15/00, 15/63, 15/00; A61K 38/17, 38/16; C07K 16/00; C12P 21/02; C12Q 1/68; G01N 33/68  
US CL : 536/23.1, 23.5; 435/320.1, 440, 252.3, 69.1, 6, 7.1; 530/350, 387.1; 514/12

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 536/23.1, 23.5; 435/320.1, 440, 252.3, 69.1, 6, 7.1; 530/350, 387.1; 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SIMMEN et al, Gene number in an invertebrate chordate, <i>Ciona intestinalis</i> , Proc. Natl. Acad. Sci. USA, Vol. 95, pages 4437-4440, see entire document.	1, 2, and 5-16



Further documents are listed in the continuation of Box C.



See patent family annex.

<p>* Special categories of cited documents:</p>		<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p>	
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

12 July 2002 (12.07.2002)

Date of mailing of the international search report

02 AUG 2002

Name and mailing address of the ISA/US

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